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EVALUATION OF THE RELATIONSHIP BETWEEN CENTRALITY AND INDIVIDUAL-LEVEL CHARACTERISTICS AMONG PWID

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BY

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ABSTRACT

Background: People who inject drugs (PWID) are a well-identified risk population for HIV infection. The risk networks of PWID have been implicated as possible modulators of both HIV risk and educational interventions among this population. In order to further understand the nature of risk networks, we examined how individual characteristics were associated with influential network position based on high closeness, betweenness, or eigenvector network centrality. These centrality measures assess an individual's importance or potential to influence others based on their connections, closeness is based on proximity to others, betweenness on acting as an intermediary between others, and eigenvector on connection to highly connected peers.

Methods: Using data from Athens, Greece collected as part of the Transmission Reduction Intervention Project (TRIP), we constructed a risk network and identified individuals in the top quartile of the distribution for each centrality measure. Using logistic regression, we identified associations between being in the top quartile of each centrality measure and individual characteristics such as demographics, risk behaviors, and altruistic behaviors. We also performed a series of sensitivity analyses to evaluate robustness of the results to the definition of high centrality (e.g., the top 50%, 20%, and 10% of the distribution of the centrality measure).

Results: The TRIP study contained a total 356 individuals after restriction to the largest connected component and censoring of individuals with missing covariate information a sample of 231 PWID was extracted from the TRIP study population. Individuals who injected at least once per day were more likely to have high closeness

(odds ratio (OR) = 3.36; 95% confidence interval (CI) = 1.57, 8.42), betweenness (OR = 2.22 95% CI = 1.06, 4.67), or eigenvector centrality (OR = 4.50 95% CI = 1.89, 10.68). Individuals who engaged in sex without a condom were less likely to have high closeness centrality (OR = 0.18 95% CI =0.07, 0.45) or high eigenvector centrality (OR = 0.19 95% CI =0.07, 0.49). Individuals who reported higher numbers of sex partners were more likely to have high betweenness centrality (OR = 1.04 95% CI =1.00, 1.08). Years living in the project recruitment area was also associated with high eigenvector centrality (OR = 1.04 95% CI = 1.00, 1.09).

Conclusions: Injection frequency was consistently related with network position and likely indicates that individuals who inject more frequently have more interactions with other PWID. Unprotected sex was also related to network centrality and may reflect that less central individuals may have less exposure to public health outreach about risk reduction, including condom use. Work to identify how individual characteristics relate to the underlying structure of PWID risk networks may provide insight into how to improve public health responses to future HIV outbreaks by identifying people of interest, who make be integral to possible transmission routes or who may be missed by standard outreach approaches.

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PREFACE

The manuscript format is being used for this thesis and is a single manuscript. The manuscript below has not been published and is not pending publication at this time. The text of the manuscript is formatted according to the standards of the journal *Substance Use & Misuse*. We examined the relationship between influential network position and individual characteristics. We used methods from the network science literature to identify individuals who connect to others in a way that suggests that they have the capacity to influence the spread of information or alter the spread of infectious disease among their peers. Primary results are included with the text and sensitivity analyses are included in the appendix.

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CHAPTER 1

Evaluation of the relationship between centrality and individual-level characteristics among PWID

by

Benjamin Skov, Ashley Buchanan, Natallia Katenka, Georgios Nikolopoulos, Samuel Friedman

Is prepared for submission to the journal *Substance Use & Misuse*.

Abstract

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Keywords: Network Centrality, Injection drug use, HIV Risk Networks, HIV risk, People who inject drugs

Introduction

Athens, Greece experienced an HIV outbreak among injection drug users starting in 2011, partially driven by the economic crisis affecting the country.[1] The recession led to dramatic loss of employment and increases in homelessness, which destabilized the injection drug using community of the city with an influx of new members. It is suspected that these changes led to previously isolated subpopulations sharing HIV risk behavior, creating new pathways for the spread of HIV.[1] Several analyses of the epidemic including molecular analysis of transmission clusters and population surveys provided support that the recent changes in the structure of the injection community contributed to the increased spread of HIV.[2, 3] The economic crisis also led to reductions in funding for harm prevention services which were already overextended, with needle exchange programs providing an average of 43 syringes per PWID per year, and opioid substitution programs having wait lists of over 4 years.[4]

Network-based studies of HIV risk networks aim to investigate both how social networks influence risk and how potential interventions affect peers.[5] Due to the relatively limited avenues for HIV transmission, an individual's possible risk connections can be identified and accurately recorded as a network, comprised of partners who have engaged in shared risk behaviors, such as sharing of syringes or unprotected sexual intercourse. In comparison, an airborne disease like influenza, has many avenues for transmission and can be more easily spread between individuals through superficial interaction, which produces a risk network where every individual could have large numbers of potential risk contacts, the majority of which the individual would likely not be able to recall unless prompted ahead of time. This well

identifiable HIV risk network enables the evaluation of how risk factors impact individuals while accounting for their connections which differs from classical epidemiologic methods, which assume that each person is independent.[6]

Network-based methods are designed specifically to account for the interconnectedness of subjects which allows for evaluation of effects that are typically not considered when assuming independence between individuals to estimate population-level effects.[7] By analyzing how individual-level measurements of network properties are associated with risk factors, the impact of network structure on health outcomes can be identified in this population.[5] HIV risk networks represent the potential pathways that HIV can spread among a population and as a result, their structure can affect how HIV spreads.[7] Network structure has been implicated in some cases as the cause of abnormal infection patterns, particularly of keeping HIV infection rates low despite high rates of risk behaviors among the population.[7] This phenomenon can occur when network structure isolates uninfected individuals from infected individuals either directly by having disconnected subnetworks or indirectly via bottlenecks or the firewall effect.[7,8,9] Bottlenecks occur when a risk network has few connections between groups, this structure limits the pathways that an infection can spread between groups which slows the spread or can even block it if those particular connections are unable to transmit infection.[9] The firewall effect is a protective phenomenon where individuals without HIV are separated from highly infectious individuals by individuals who have HIV but have low viral loads, either due to treatment or natural disease progression.[8] These individuals with low viral load have a relatively low risk of infecting new individuals while engaging in risk

behaviors and act as a barrier that blocks or dramatically reduces the spread of HIV to their uninfected partners.[8,10] Unfortunately, network based studies have some limitations in particular the amount of field work required to recruit subjects and successfully identify their contacts.[11] Additionally, this is a stigmatized population and injection drug use is illegal in many parts of the world so individuals may be hesitant to identify their partners.[11]

It has been broadly asserted and demonstrated in practice that interventions designed to incorporate network structure, such as the training of peer educators, could be effective in this population.[5,12] Variants of the peer educator intervention have been tested in several contexts and with sample sizes ranging from 25 to over 500 subjects.[12] These reports have shown broadly beneficial results on various HIV related outcomes with the majority of studies focusing on reductions in HIV risk behavior.[12] Studies have also investigated the impact of peer interventions on antiretroviral adherence and retention in care, which are well-known challenges in the treatment of HIV.[13] The underlying principle of these interventions is that providing education to an individual enables them to share this knowledge with their peers and that individuals can be trained to enhance this transfer of knowledge.[12] Education from peers has been shown to be more persuasive than education directly from a health provider.[12] Additionally, this type of intervention can affect individuals who have limited direct contact with health care providers or public health initiatives, and thus have limited benefit from interventions delivered directly by those groups. Because the intervention is provided to individuals in the network then the benefit of the intervention can spread to their contacts who then in turn could further spread the

effects, the position of these initial individuals in the network likely influences how effective this type of intervention is among the population of interest. Only a small amount of research has been done to identify which individuals in the network optimize the effects of these interventions, such as reduction in risk behavior or increases in education, or how patient covariates could affect the spread of information from person to person[14,15,16]

Recent work has identified that some network properties such as network density, how interconnected an individual's risk partners are, and network centrality, a measure of positional influence, are related to HIV risk behaviors, such as drug equipment sharing.[17] In addition, a study of injection drug users in Melbourne, Australia at risk for Hepatitis C infection has shown that several network structural measures, particularly eigenvector centrality, a measure of having well connected contacts, were associated with increased rates of infection and higher injection frequency.[18] Another study of drug users in the Appalachian region in the United States also identified a similar association between Hepatitis C infection and elevated eigenvector centrality. [19] The results of these studies suggest that network centrality could be associated with HIV risk because it shares similar transmission pathways with Hepatitis C.

The importance of an individual's position in a network is an area of ongoing study and several measurements have been proposed in the network literature. Three well established measures are closeness centrality, betweenness centrality, and eigenvector centrality. These measures each have a different way of defining important positions in the network. Each centrality measure defines a value for each

individual in the network based on the positions of others and the connections between them, and formal definitions are presented in Appendix 1.

Closeness centrality is based on the lengths of the shortest path between an individual and each other individuals in the network along existing connections.[20] The resulting measure scales from 0 to 1 with a higher value indicating that an individual is closer to the other individuals of the network, implying a central position.[20] The importance that closeness centrality is measuring is how well an individual is able to reach the rest of the network. In a public health context, this could be used to identify people who are at high risk of catching a communicable disease or someone who could easily spread information to the entire population.

Betweenness centrality measures how many pairs of individuals are connected in part by a given third individual. It is calculated by determining the shortest path between each pair of individuals in the network then identifying how many of those paths cross through a given individual.[20] The resulting measure increases as an individual is part of more of these shortest paths, indicating a central position in the flow of information through the network.[20] The importance measured by betweenness centrality is how much an individual enables transmission through the network. Individuals with high betweenness centrality act as gatekeepers in the network, and in the context of HIV, are people who bridge relatively isolated groups. If these individuals remain uninfected, by avoiding risk behaviors, through medical intervention, or if they have suppressed HIV viral loads, they would limit or slow the spread of infection in the population.

The third centrality measure is eigenvector centrality. This measure involves the eigen decomposition of a matrix representation of the network and produces a value for each individual that indicates how well connected the individual is, as well as how well connected their direct contacts are to the rest of the network.[21] Individuals with high values for this measurement are important because they have influential contacts, in the sense that these contacts have influence on the rest of the network due to how they connect to the rest of the network. In public health interventions, these individuals may be highly effective peer educators because they can educate many influential individuals who then are very able to further spread information.

The intent of this study is to expand the current knowledge base about how individual characteristics relate to an individual's position in an HIV risk network. Several studies have investigated the impact of social network members on various HIV risk factors and HIV risk itself, but further research is needed to better understand measures used to assess the position of individuals in the network and how it relates to individual-level features and behaviors.[22,23] This study will add to the evidence base about how position in the network relates to individual-level characteristics by examining the relationships between network centrality measures and patient characteristics in a risk network of people who inject drugs. Specifically, this study will evaluate if certain individual characteristics, such as duration of drug use or housing status, are associated with important network positions. These associations could then be further explored to see if there is possibly an underlying process by which individual characteristics and network position are interrelated or to identify

individuals who are likely to be central without necessarily having to ascertain the full network structure.

Materials and Methods

Study population

The study population used for this analysis comes from the Transmission Reduction Intervention Project (TRIP), a public health project conducted in Athens, Greece from 2013 to 2015 that recruited a total of 356 PWID.[24] The study initially recruited injection drug users who had recently been infected with HIV, as well as those who had long-standing infections. These initial seed recruits were referred to the study by testing facilities. The largest source of seed recruits was ARISTOTLE, a large multi-wave respondent driven sampling outreach program which ran from August 2012 through the end of 2013, which overlapped with TRIP.[25] Each enrollee was asked to identify and refer all individuals who had been present or participated any time that they had injected drugs or had sex in the last 6 months. Each of those contacts who were successfully identified and agreed to participate were asked to identify their injection or sexual partners during the past 6 months as well. If any contact was identified as recently HIV infected their contacts and contacts of contacts were identified, as if they had been one of the initial enrollees. If one of the subjects identified a contact already enrolled in the study this connection was confirmed and added to the data. In addition field staff identified a small number of connections that were observed during recruitment but not reported by participants. The resulting recruited population was a sample of the HIV risk network of Athens, Greece made up of individuals recently diagnosed with HIV infection, their contacts and the contacts of

those contacts. This was represented by a network graph with edges representing potential sexual or injection transmission connections between the subjects. Each subject completed a computer-assisted survey about their risk behaviors, drug use history, opinions and experiences related to HIV and access to health care services. Subjects with newly-diagnosed HIV infections were provided with case management services and referrals to care. This analysis restricts itself to only those subjects in the largest connected component of the network and only the first study visit of each subject. A connected component is a smaller network within a larger network where all of the nodes are able to trace a path to all other members of the component, either through direct connections or through a series of other nodes. The TRIP network contains several components with the largest containing two-thirds of the study population. This restriction was necessary due to the centrality measures not being identifiable in a network that has multiple components.

Statistical analyses

Centrality measures were calculated for each individual based on their definitions and participants with high centrality were identified, where high centrality was defined as being in the upper quartile for that measure. The choice to use this definition of relative high centrality rather than an absolute definition was based on the non-normal distributions of betweenness and eigenvector centrality and the goal of examining individuals who are central compared to their peers. Associations were assessed initially with univariate logistic regression models for each covariate and centrality measure. Then, we fit a single multivariable logistic model for each centrality measure using all of the covariates included in the univariate models. As a sensitivity analysis,

each multivariable model was redefined with high centrality defined as being above the 50th, 20th, and 10th percentile in order to assess consistency of estimated associations to this threshold. Covariates included patient demographics, substance use history, self reported risk behaviors in the last 6 months, and frequency of providing aid to close contacts. HIV status was specifically not included as a covariate since the sampling method of TRIP was based on HIV infection status which could confound the association between high centrality and HIV infection. Individuals with missing information were assumed to have information missing completely at random and were censored after centrality measures were calculated. They were censored after network properties were calculated in order to avoid inducing measurement error in the centrality measures by altering the observed network structure.

Results

Participant demographics

After restriction to the largest connected component of the risk network and removal of 10 (4%) subjects with missing baseline covariate information, there were 231 individuals included in the final sample; that is, 65% of the original 356 subjects recruited in TRIP. For the determination of centrality measures the entire largest connected component of 241 individuals was used and contained 502 connections between members, with 95% of them being confirmed by subject reporting. Distributions of the baseline covariates are displayed in Table 1. The majority of the subjects were male (80%) and between the ages of 25 and 40 years. They were predominantly Greek in ethnicity (88%), unemployed (70%) and the majority were

either homeless (29%) or had unstable housing (54%). In terms of HIV risk behaviors, over half of the individuals injected at least once per day and over three quarters had shared injection equipment in the last six months. The number of injection and sex partners in the last six months varied considerably. Over 85% of individuals had 10 or fewer injection partners but 7 subjects reported over 100 partners. Reported number of sex partners was similar with 94% of subjects reporting 10 or fewer partners but 7 individuals reported over 50 or more partners in the last 6 months.

Associations between high centrality and individual characteristics

Closeness centrality

The full results from the univariate and multivariable models for high closeness centrality are shown in Table 3 and the associated sensitivity analyses are reported in appendix 2. In the univariate models, individuals were more likely to be classified as high centrality, defined as the top 25%, for each additional injection partner they reported (odds ratio (OR) = 1.02, 95% confidence interval (CI) = 1.01, 1.04) or if they were homeless rather than stably housed(OR = 3.02; 95% CI = 1.11, 8.24). Individuals who injected at least once per day had an estimated 3.8 times the odds of being considered high centrality (95% CI =1.88, 7.67), compared to those who injected less frequently. Subjects who participated in sex without a condom were less likely to be high centrality with an estimated odds ratio of 0.26 (95% CI = 0.13, 0.53). Two statistically significant associations were observed in the adjusted models, specifically daily injection drug use was associated with higher odds of being high centrality and having sex without a condom was inversely associated with high

closeness centrality with estimated odds ratios of 3.64 (95% CI = 1.57, 8.42) and 0.18 (95% CI = 0.07, 0.45), respectively.

The sensitivity analyses for high closeness centrality identified a statistically significant odds ratio for the association between daily injection and high centrality when high centrality was defined as the top 50%, top 20%, and top 10%,. The inverse association between condomless sex and high closeness centrality was also significant in all of the sensitivity models. Of note, all of the sensitivity analyses also identified an association between higher than a high school education and high closeness centrality with estimated odds ratios ranging from 3.1 to 4.74 compared to not having a high school degree, despite this not being present in the primary analysis.

Betweenness centrality

The full results from the univariate and multivariable models for high betweenness centrality are shown in Table 4 and the associated sensitivity analyses are reported in Appendix 2. In the univariate models, individuals were more likely to be classified as high betweenness centrality if they had a higher number of sex partners with an estimated 4% increase in the odds (95% CI = 1.01, 1.07) for every additional reported sex partner. Additionally, these models indicated that individuals who injected at least daily had an estimated 2.4 times the odds of having high betweenness centrality (95% CI = 1.25, 4.46). The multivariable model had somewhat similar results. Individuals with more sex partners had 1.04 times the odds to be highly central (95% CI = 1.00, 1.08) per additional partner and individuals who injected at least daily were more likely to be highly central compared to those who injected less often (OR = 2.22 95% CI = 1.06, 4.67). In the sensitivity analyses for different

thresholds for high betweenness centrality the only consistent association was the 20% threshold for the outcome, which was also associated with a higher number of sex partners (OR = 1.06 95% CI = 1.00,1.13).

Eigenvector centrality

The full results from the univariate and multivariable models for high eigenvector centrality are shown in Table 5 and the associated sensitivity analyses are reported in Appendix 2. The univariate models for eigenvector centrality showed three statistically significant associations. Individuals who had helped their friends seek drug treatment less than once per week were less likely to be highly central than those who had never helped their peers seek treatment (OR 0.43; 95% CI = 0.21, 0.87). Individuals reporting sexual intercourse without a condom were less likely to be classified as high eigenvector centrality with an odds ratio of 0.33 (95% CI = 0.17, 0.64). Lastly injecting drugs at least once per day was associated with an estimated 3.5 times the odds of being highly central, compared to less frequent injection (95% CI = 1.74, 6.88). The multivariable model identified similar associations with injection frequency and occasionally helping peers seek substance treatment with odds ratios of 4.50 (95% CI = 1.89, 10.68) and 0.29 (95% CI = 0.12, 0.71), respectively. Individuals with high eigenvector centrality were also noted to have lived in Athens for more years (OR = 1.04; 95% CI = 1.00, 1.09) and to be more likely to live with a sexual partner (OR = 3.75 ;95% CI = 1.34, 10.47). Individuals who engaged in sex without a condom were also approximately 5 times less likely to be considered highly central (OR = 0.19; 95% CI = 0.07, 0.49).

Sensitivity analyses showed that the relationship between condom use and high centrality was comparable at each threshold for defining high eigenvector centrality with odds ratios ranging from 0.16 (95% CI = 0.04, 0.78) to 0.23 (95% CI = 0.08, 0.62). The association between daily injection and high eigenvector centrality was identified in models with high centrality defined as the top 50% (OR = 5.81 95% CI = 2.77, 12.16), 20% (OR = 5.39 95% CI = 2.05, 14.16), and 10% (OR = 9.51 95% CI = 2.05, 44.12) of subjects. High centrality was also associated with the number of years living in Athens in both the 20% and 10% sensitivity analyses.

Discussion

The most prominent results of our analysis were those related to the risk factors injection frequency and condom use. All of the centrality measures identified that highly central individuals were more likely to inject more often. Both closeness and eigenvector centrality showed this association was consistent regardless of the exact definition of high centrality. A large portion of this network was comprised of connections defined by injection drug use, so individuals who inject more frequently have more opportunities to have injection partners and spend more of their time acquiring and using drugs, which could lead to becoming more connected to other PWID. Earlier work by Spelman, et al. identified that changes in closeness and eigenvector centrality were associated with increases in injection frequency over time. The strong association between condom use and closeness and eigenvector centrality has a more situational explanation. At the time, TRIP was conducted there were several large-scale HIV prevention initiatives happening in Athens, all of which disseminated information about risk reduction. Closeness and eigenvector centrality

can both be interpreted as a measurement of how easy it is for information in the network to reach an individual.[20,21] Thusly, it is not unreasonable to consider that highly central individuals were more likely than their less central peers to be exposed to public health messages, such as the importance of condom use and to have access to condoms being distributed by outreach workers. Less central individuals may have been less likely to receive such messages or be less aware of the current outbreak and therefore may have taken fewer preventative measures.

Another result of interest is the minimal support for the associations between covariates and betweenness centrality . The primary model for betweenness centrality showed only two associations, injection frequency as mentioned above and the number of sexual partners. The association between number of sex partners and betweenness centrality could indicate that while injection behaviors made up the majority of the network, sexual connections also play a role in the connectivity of this population. Betweenness centrality is often related to individuals who act as bridges connecting groups, so an association between this measure and sexual connections could imply that sexual connections may have a role in bridging otherwise disconnected groups. If this is the case, then increases in sexual risk reduction such as condom use could increase the fragmentation of the network or slow the spread of HIV via bottlenecking.[9] However the sensitivity analyses did not strongly support either of these associations or indicate any other consistent patterns of associations. This implies that there might be a limited relationships between individual characteristics and betweenness centrality. This is quite possible since betweenness centrality is highly affected by the connection structure of individuals far away from

an individual, which is unlikely to be influenced by the individual. This contrasts with closeness and eigenvector centrality which are more influenced by the direct connections an individual has.

The relationship between eigenvector centrality and time spent living in Athens is a novel association and has a relatively straightforward possible mechanism. Similar to how injection frequency creates more opportunities to connect to other members of the community, living in an area allows an individual to accumulate more interactions especially to others who have also remained in the community for a longer time since interactions are two sided. This aligns with the core interpretation of eigenvector centrality, connectivity with other well-connected individuals.

An extended body of literature has examined the structure of social and risk networks of PWID as they relate to HIV risk. These studies have identified various network based risk factors for HIV such as K core membership, which indicates being part of a highly interconnected region of a network, and changes in network composition over time.[22,26] However, this area of research is still growing, and research methods vary considerably across studies with various definitions used to define risk networks. Some studies use potential risk contacts such as in TRIP, others restrict the network to only actual risk partners, and some studies collect network data by asking recruited individuals to describe their contacts but don't recruit these contacts.[22,24,27] These different definitions capture different amounts of information about the community being surveyed and their results must take this into consideration. Additionally, relatively little work has been done to examine the determinants of network structure such as the processes by which networks grow and

change over time. Changes in network structure over time have been observed and linked to changes in risk behaviors but these relationships have not been fully explored.[18] In this work, we have examined how network structure is related to the individual characteristics, providing a starting point for future investigations into how network structure develops.

Limitations

This work has several limitations. A major concern is the representativeness of the recruited network of PWID. The Transmission Reduction Intervention Project was intended to test if contact tracing of individuals who were recently infected with HIV was an effective method for detecting new cases of HIV.[24] As a result, the sample started recruitment from individuals who were identified as HIV infected by public health initiatives. These individuals and their contacts may not represent the full population of injection drug users in Athens, but instead were a sample of those who became HIV infected during the outbreak and their contacts. The specific sampling procedure used led to the network being centered on individuals infected with HIV. Another possible challenge with the network structure used in this work is that collection of information on the connections was completed over a two year period. This long time period was necessary given the complexities of the recruitment procedure but may reduce our confidence in the results. It is quite possible that the structure of the connections between individuals may have changed over these 2 years so the network structure used in this analysis may be different from the actual network at any single point in time. The injection drug community in Athens at the time of the study may differ from many other populations in other major cities due to the unique

conditions of the economic crisis starting in 2008. National financial instability led to increases in unemployment and homelessness combined with reduction in public services. These factors led to increases in the number of individuals participating in injection drug use and destabilized preexisting risk networks in the city. As a result, the network observed in TRIP may not be representative of populations who have been relatively stable for an extended period. Instead, the results may be more applicable to populations experiencing similar economic recessions and subsequent rises in injection drug use. Another limitation was that due to the network structure individuals are not truly independent of each other which is a basic assumption of the statistical methods being used. While we would have preferred to use a method that accounted for this potential lack of independence, methods for addressing the specific issues of this study are not fully developed. Finally we were not able to fully address the small amount of missing covariate information in the study. We chose to perform a complete case analysis since the amount of individuals with missing information was very small(4%) and statistical methods for addressing missing data in networks do not exist at this time.

This study also has some strengths. We were able to analyze a large number of potential covariates collected by the TRIP study including information about the number of connections that were not directly recruited to the study. The study also had a very clearly defined geographic region, Athens, Greece, and this led to recruitment from a well-defined population. We also examined several centrality measures with identical methodology which provide a broader set of results. Our choice to use relatively high centrality rather than model the exact value of centrality

had several advantages. The first is that it avoided the complexities of the non normal distributions of the betweenness and eigenvector centrality which posed significant challenges to modelling. Additionally the relative measure is less precise which may have mitigated some of the potential measurement error from the network not being consistent during the entire recruitment period. Thirdly, the exact value of an individuals centrality is very sensitive to changes in the network which makes it challenging to interpret them out of context. The relative measure we used compares individuals to the other members of the network, identifying individuals who are relatively high compared to the average. These above average individuals are likely to be of interest regardless of their exact centrality value and may be more consistently identifiable under small changes in the observed network. We also performed sensitivity analyses in order to account for the relatively arbitrary selection of the top 25% threshold for "high centrality". This allowed us to confirm that key results were not simply due to the selected cutoff but were truly related to relatively high centrality in the network.

Future work

Future work in this area will include corroborating these results in other networks of PWIDS from other regions or time points to identify if these patterns are unique to the context of TRIP or if similar patterns exist among other PWID communities. By examining the relationships between central positions in a network and individual characteristics in multiple contexts, it would be easier to identify which effects are specific to certain groups and which could be general features of PWID. If any such associations are consistent across certain groups, this could provide insights into the

processes that underlie the formation of these networks. With adequate longitudinal data on an HIV risk network the impact of individual covariates on changes in network structure over time which could provide insight into the trajectory of PWID and how these networks develop and evolve. This information could be used to intervene on individuals at risk for dangerous trajectories or possibly even on the growth of HIV risk networks themselves. Another extension would be to attempt to fit models to predict highly central individuals without needing to necessarily observe the full network. If such models were reliable enough, they could be used to screen for key individuals in a population. This would be valuable for implementing peer interventions or otherwise leveraging network structure in areas where it is not practical or feasible or there are inadequate resources for full contact tracing.

Conclusions

In conclusion, these results show that influential positions in the risk networks of PWID are associated with individual features and behaviors. In particular, risk behaviors themselves seem to be major factors in the connectivity of individuals. This expands the current understanding of PWID network dynamics and lays groundwork for examining the underlying processes that create these networks. Further work should be done to identify if these relationships are consistent across contexts and cultures and if they are reliable enough to be used to identify influential community members as part of public health initiatives.

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Table 1. Baseline Characteristics of Participants Enrolled in the Transmission Reduction Intervention Project, Athens, Greece, 2013-2015 (N = 231)

Continuous Characteristics	Mean (standard deviation)
Age (years)	36 (8.1)
Age at first injection (years)	22 (8.2)
Years injecting	13 (8.1)
Self-reported number of injection partners	10 (19)
Self-reported number of sex partners	3.8 (9.5)
Number of successfully recruited partners	4 (3.5)
Years lived in Athens	28 (13.1)
Categorical Characteristics	**n (%)**
Frequency of injection over the last 6 months	
Less than daily	101 (44%)
At least once per day	130 (56%)
Employment status	
Working	33 (14%)
Unemployed	161 (70%)
Other (student, homemaker, etc.)	37 (16%)
Shared injection equipment in the last six months	181 (78%)
Condomless sex in the last six months	101 (44%)
Infected with HIV	123 (53%)
Ever been tested for HIV	215 (92%)
Gender	
Male	185 (80%)
Female	46 (20%)
Ethnicity	
Greek	204 (88%)
Non-Greek	27 (12%)
Housing status	

Stable	36 (16%)
Unstable	126 (54%)
Homeless	69 (29%)
Education	
Less than high school diploma	144 (62%)
High school diploma	55 (24%)
College or other advanced education	32 (14%)
Relationship status	
Single	184 (80%)
Living with partner	47 (20%)
Helped contacts with finding treatment for substance use issues	
Never	68 (29%)
Occasionally	106 (46%)
At least once per week	57 (25%)
Helped contacts with financial support	
Never	92 (40%)
Occasionally	103 (45%)
At least once per week	36 (16%)
Helped contacts with finding a place to sleep	
Never	103 (45%)
Occasionally	107 (46%)
At least once per week	21 (9%)

Table 2. Estimated Odds Ratios (OR) of the Association Between Individual Characteristics and Membership in the top quartile of the distribution of Closeness centrality with Corresponding 95% Confidence Intervals (CIs) among Participants Enrolled in the Transmission Reduction Intervention Project, Athens, Greece, 2013-2015 (N = 231)

	Univariate Models		Multivariable Models	
Individual Characteristics	OR	95% CI	OR	95% CI
Age (years)	0.996	0.960, 1.034	0.987	0.927, 1.050
Years injecting	0.980	0.943, 1.015	0.989	0.939, 1.041
Self-reported number of injection partners	**1.021**	**1.006, 1.036**	1.010	0.991, 1.030
Self-reported number of sex partners	1.022	0.994, 1.051	1.015	0.973, 1.058
Years lived in Athens	0.990	0.968, 1.013	1.008	0.971, 1.046
Frequency of injection over the last 6 months				
Less than daily	Ref		Ref	
At least once per day	**3.795**	**1.877, 7.670**	**3.637**	**1.570, 8.424**
Employment status				
Working	Ref		Ref	
Unemployed	2.369	0.725, 7.743	2.145	0.625, 7.366
Other (student, homemaker, etc.)	1.851	0.670, 5.116	1.136	0.268, 4.812
Shared injection equipment in the last six months	0.887	0.432, 1.820	0.521	0.206, 1.315
Condomless sex in the last six months	**0.264**	**0.130, 0.533**	**0.178**	**0.071, 0.447**
Gender				
Male	Ref		Ref	
Female	1.699	0.838, 3.448	1.790	0.636, 5.042
Ethnicity				
Greek	Ref		Ref	
Non-Greek	2.020	0.866, 4.715	1.335	0.365, 4.883
Housing status				
Stable	Ref		Ref	
Unstable	1.176	0.440, 3.144	0.977	0.281, 3.397
Homeless	**3.023**	**1.109, 8.240**	1.413	0.391, 5.099

Education				
Less than high school diploma	Ref		Ref	
High school diploma	0.407	0.170, 0.976	0.730	0.256, 2.083
College or other advanced education	1.461	0.645, 3.312	2.604	0.954, 7.107
Relationship status				
Single	Ref		Ref	
Living with partner	0.811	0.374, 1.758	1.790	0.645, 4.967
Helped contacts with finding treatment for substance use issues				
Never	Ref		Ref	
Occasionally	0.878	0.430, 1.791	0.836	0.344, 2.032
At least once per week	1.071	0.479, 2.398	0.829	0.290, 2.367
Helped contacts with financial support				
Never	Ref		Ref	
Occasionally	0.978	0.494, 1.937	1.103	0.477, 2.553
At least once per week	2.291	0.996, 5.271	2.765	0.937, 8.157
Helped contacts with finding a place to sleep				
Never	Ref		Ref	
Occasionally	1.452	0.764, 2.757	1.487	0.654, 3.380
At least once per week	1.562	0.540, 4.514	0.633	0.149, 2.687

Table 3. Estimated Odds Ratios (OR) of the Association Between Individual Characteristics and Membership in the top quartile of the distribution of Betweeness centrality with Corresponding 95% Confidence Intervals (CIs) among Participants Enrolled in the Transmission Reduction Intervention Project, Athens, Greece, 2013-2015 (N = 231)

	Univariate Models		Multivariable Models	
Individual Characteristics	OR	95% CI	OR	95% CI
Age (years)	0.969	0.933, 1.007	0.969	0.912, 1.030
Years injecting	0.975	0.938, 1.012	0.994	0.946, 1.044
Self-reported number of injection partners	1.009	0.995, 1.023	0.998	0.978, 1.018
Self-reported number of sex partners	**1.040**	**1.010, 1.062**	**1.041**	**1.001, 1.083**
Years lived in Athens	0.995	0.973, 1.018	1.016	0.979, 1.053
Frequency of injection over the last 6 months				
Less than daily	Ref			
At least once per day	**3.358**	**1.246, 4.463**	**2.221**	**1.056, 4.671**
Employment status				
Working	Ref			
Unemployed	1.800	0.536, 6.050	2.426	0.745, 7.895
Other (student, homemaker, etc.)	2.172	0.790, 5.976	1.413	0.348, 5.736
Shared injection equipment in the last six months	1.739	0.788, 3.837	1.330	0.524, 3.375
Condomless sex in the last six months	0.770	0.421, 1.407	0.723	0.342, 1.528
Gender				
Male	Ref		Ref	
Female	1.361	0.668, 2.775	0.869	0.317, 2.382
Ethnicity				
Greek	Ref		Ref	
Non-Greek	0.814	0.312, 2.125	0.765	0.194, 3.021
Housing status				
Stable	Ref		Ref	
Unstable	2.111	0.756, 5.890	1.654	0.505, 5.419
Homeless	2.902	0.994, 8.475	1.636	0.448, 5.969
Education				
Less than high school diploma	Ref		Ref	
High school diploma	0.723	0.338, 1.545	1.062	0.432, 2.609
College or other advanced education	1.515	0.667, 3.438	2.399	0.911, 6.315
Relationship status				
Single	Ref		Ref	

Living with partner	0.444	0.187, 1.055	0.666	0.242, 1.831
Helped contacts with finding treatment for substance use issues				
Never	Ref		Ref	
Occasionally	0.686	0.334, 1.410	0.688	0.299, 1.586
At least once per week	1.502	0.698, 3.229	1.246	0.491, 3.166
Helped contacts with financial support				
Never	Ref		Ref	
Occasionally	0.606	0.308, 1.193	0.677	0.310, 1.479
At least once per week	1.914	0.855, 4.287	2.079	0.758, 5.707
Helped contacts with finding a place to sleep				
Never	Ref		Ref	
Occasionally	1.355	0.724, 2.537	1.160	0.548, 2.457
At least once per week	1.391	0.485, 3.993	0.608	0.153, 2.412

Table 4. Estimated Odds Ratios (OR) of the Association Between Individual Characteristics and Membership in the top quartile of the distribution of Eigenvector centrality with Corresponding 95% Confidence Intervals (CIs) among Participants Enrolled in the Transmission Reduction Intervention Project, Athens, Greece, 2013-2015 (N = 231)

	Univariate Models		Multivariable Models	
Variable	OR	95% CI	OR	95% CI
Age (years)	1.026	0.989, 1.064	0.993	0.931, 1.060
Years injecting	1.005	0.969, 1.042	1.000	0.949, 1.055
Self-reported number of injection partners	1.011	0.996, 1.025	1.003	0.983, 1.023
Self-reported number of sex partners	1.018	0.990, 1.047	1.030	0.990, 1.073
Years lived in Athens	1.018	0.994, 1.042	**1.044**	**1.002, 1.087**
Frequency of injection over the last 6 months				
Less than daily	Ref		Ref	
At least once per day	**3.463**	**1.743, 6.880**	**4.495**	**1.892, 10.680**
Employment status				
Working	Ref		ref	
Unemployed	2.000	0.542, 7.382	3.442	0.884, 13.398
Other (student, homemaker, etc.)	2.812	0.936, 8.454	0.986	0.204, 4.756
Shared injection equipment in the last six months	0.914	0.446, 1.873	0.735	0.283, 1.913
Condomless sex in the last six months	**0.326**	**0.166, 0.638**	**0.189**	**0.074, 0.485**
Gender				
Male	Ref		Ref	
Female	1.647	0.813, 3.337	1.359	0.481, 3.839
Ethnicity				
Greek	Ref		Ref	
Non-Greek	1.332	0.549, 3.231	1.897	0.483, 7.448
Housing status				
Stable	Ref		Ref	
Unstable	1.025	0.403, 2.610	1.070	0.298, 3.836
Homeless	2.354	0.901, 6.150	1.956	0.533, 7.181
Education				
Less than high school diploma	Ref		Ref	
High school diploma	0.458	0.199, 1.056	0.752	0.264, 2.141
College or other advanced education	1.224	0.532, 2.815	2.205	0.753, 6.452

Relationship status				
Single	Ref		Ref	
Living with partner	1.391	0.682, 2.836	**3.746**	**1.340, 10.474**
Helped contacts with finding treatment for substance use issues				
Never	Ref		Ref	
Occasionally	**0.427**	**0.211, 0.866**	**0.286**	**0.115, 0.710**
At least once per week	0.699	0.322, 1.516	0.550	0.194, 1.558
Helped contacts with financial support				
Never	Ref		Ref	
Occasionally	0.915	0.470, 1.782	1.528	0.640, 3.648
At least once per week	1.591	0.685, 3.694	2.957	0.933, 9.367
Helped contacts with finding a place to sleep				
Never				
Occasionally	1.001	0.533, 1.882	0.905	0.392, 2.087
At least once per week	1.248	0.437, 3.561	0.388	0.089, 1.696

Figure 1. Visualization of Transmission Reduction Intervention Project study population by HIV status, Athens, Greece, 2013-2015 (N = 356).

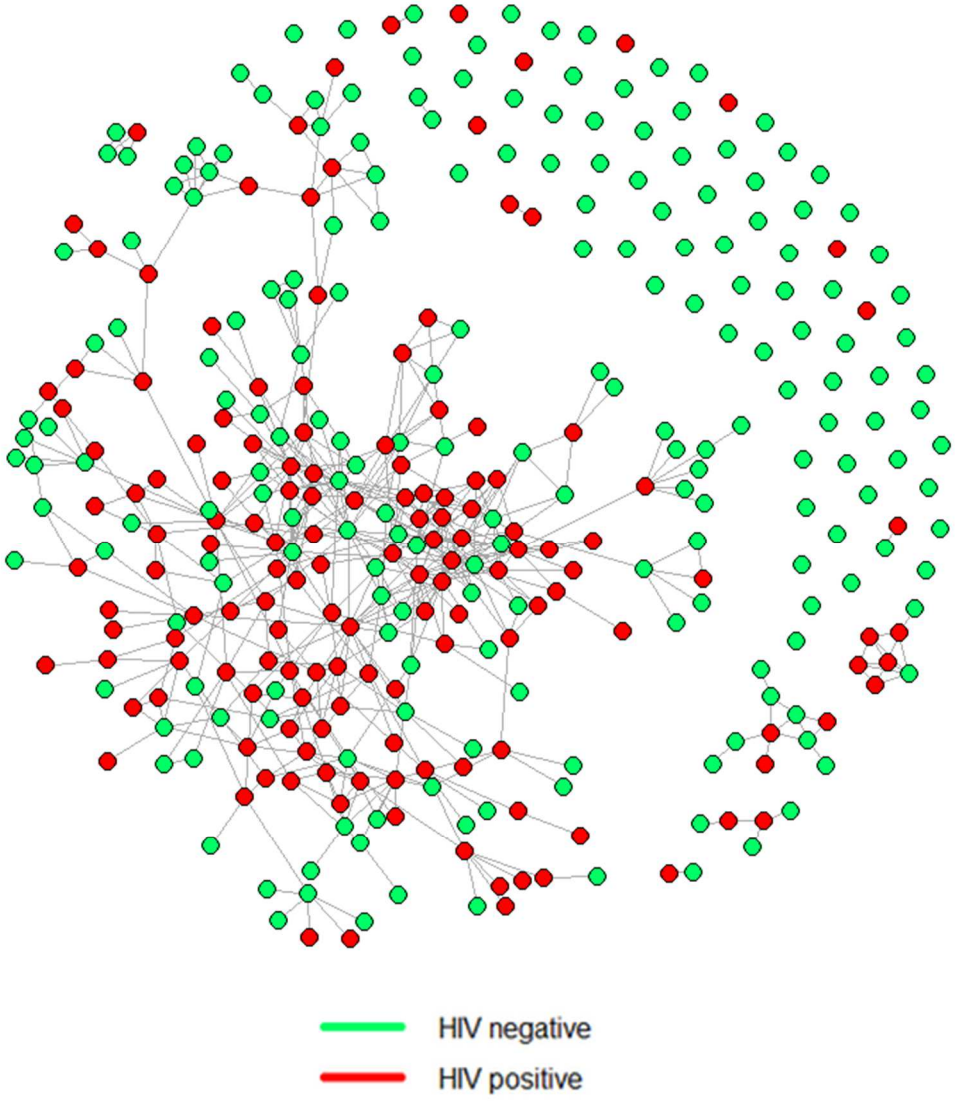


Figure 2. Visualization of the giant component Transmission Reduction Intervention Project study population by HIV status, Athens, Greece, 2013-2015 (N = 241)

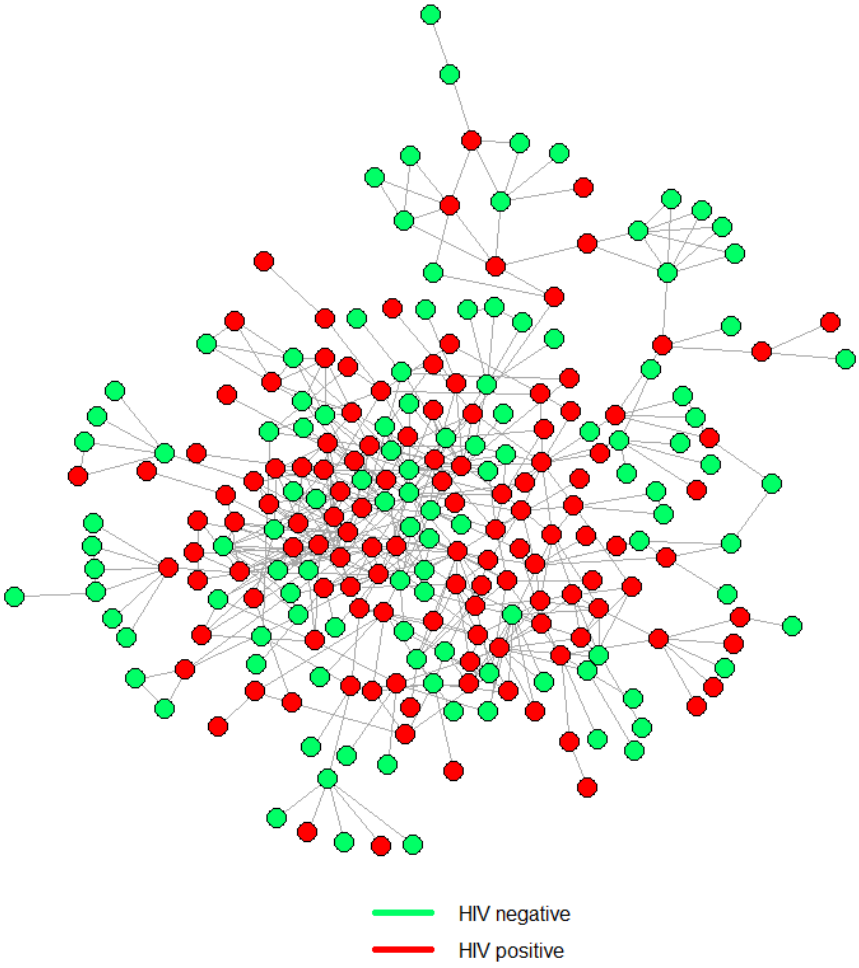


Figure 3. Visualization of the giant component of the TRIP network with node color based on closeness centrality quartiles

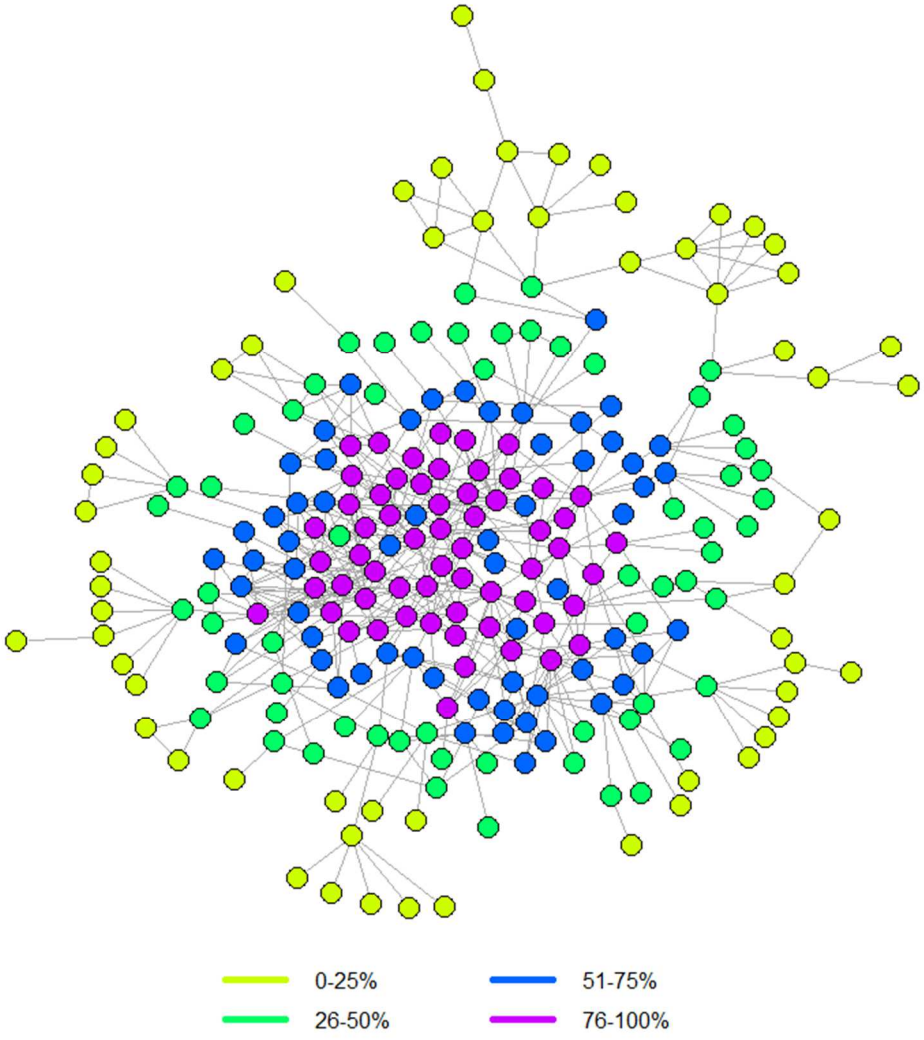


Figure 4. Visualization of the giant component of the TRIP network with node color based on betweenness centrality quartiles

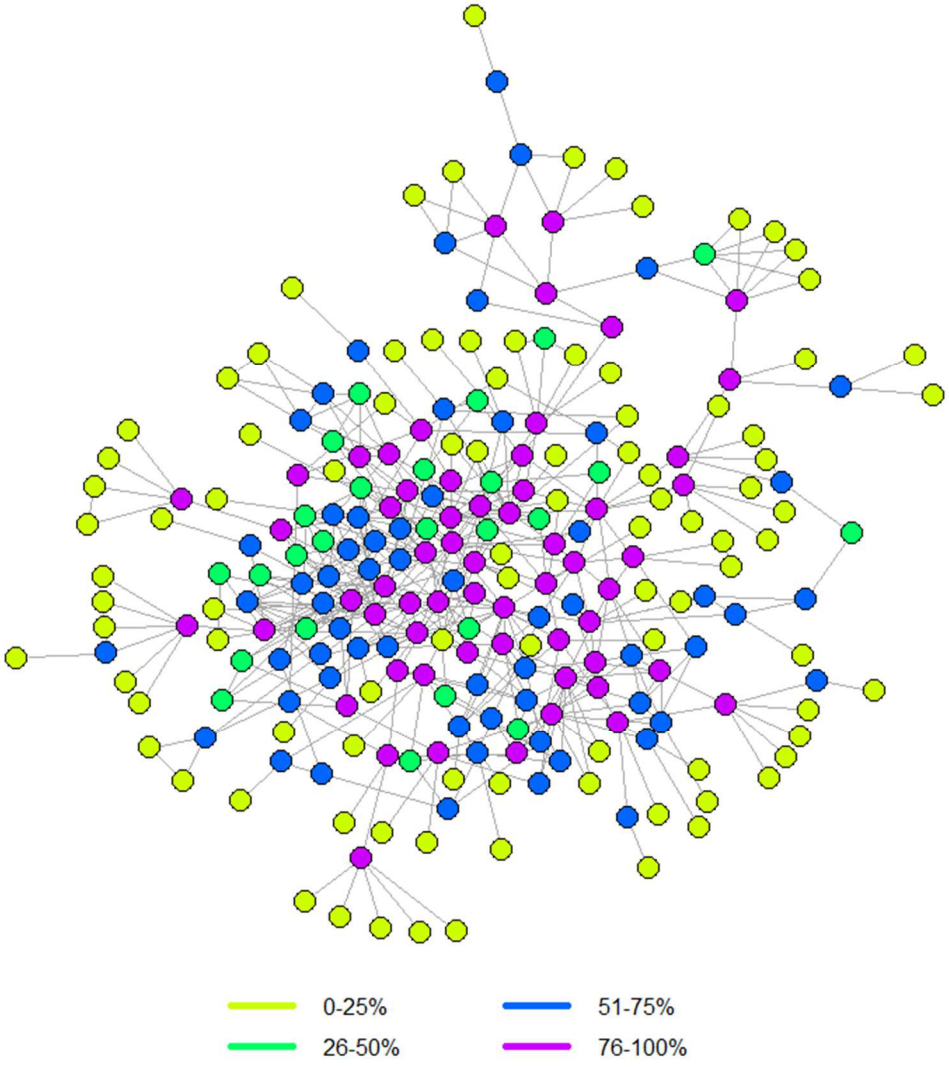


Figure 5. Visualization of the giant component of the TRIP network with node color based on eigenvector centrality quartiles

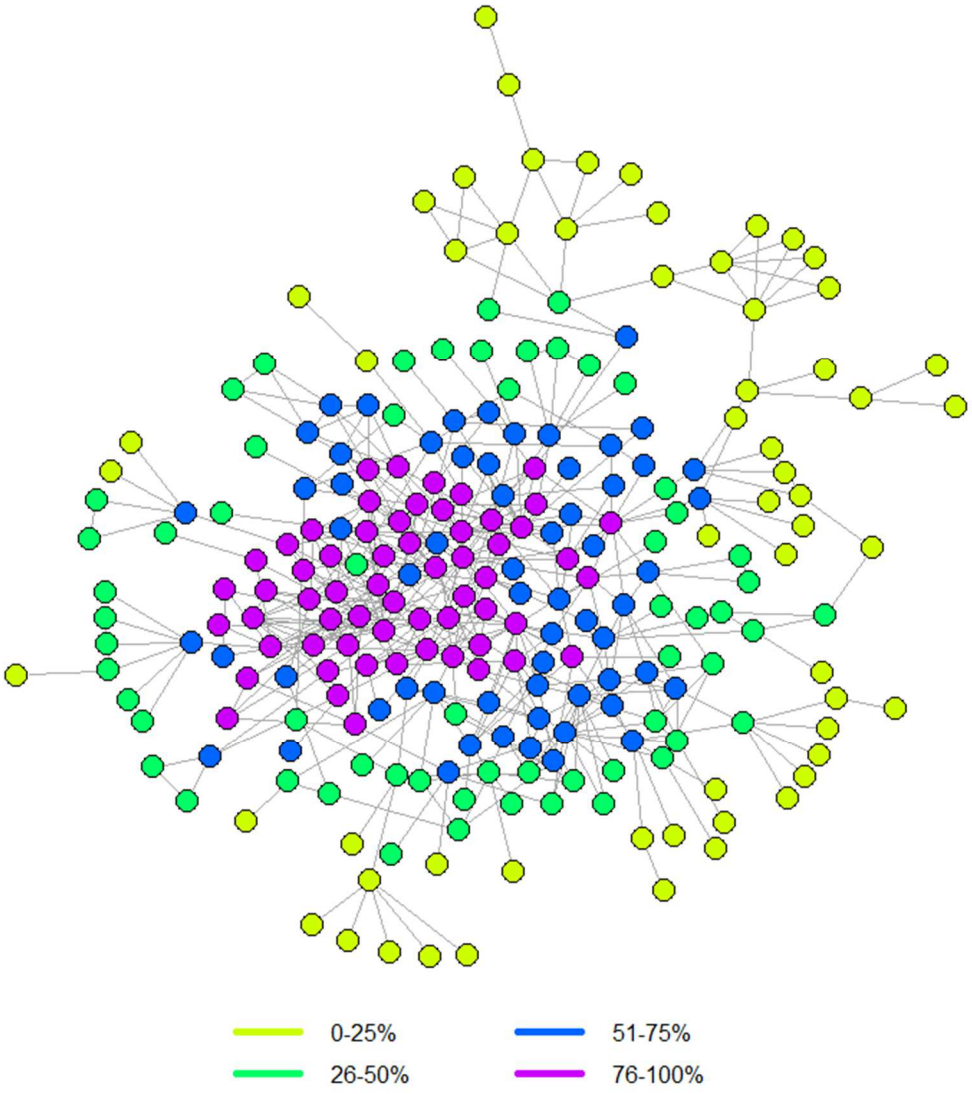


Figure 6. Forrest plot of estimated odds ratios for the association between closeness centrality in the upper quartile and individual characteristics among participants Enrolled in the Transmission Reduction Intervention Project, Athens, Greece, 2013-2015 (N = 231)

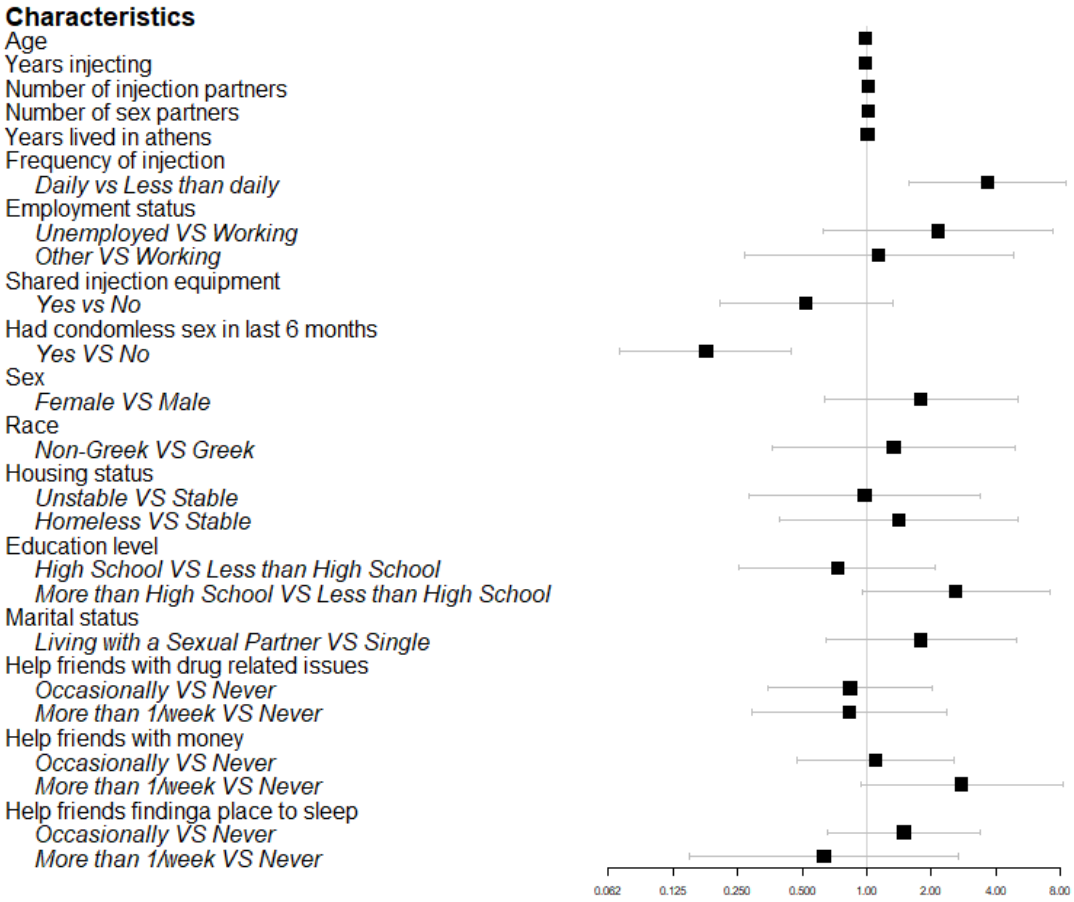


Figure 7. Forrest plot of estimated odds ratios for the association between betweenness centrality in the upper quartile and individual characteristics among participants Enrolled in the Transmission Reduction Intervention Project, Athens, Greece, 2013-2015 (N = 231)

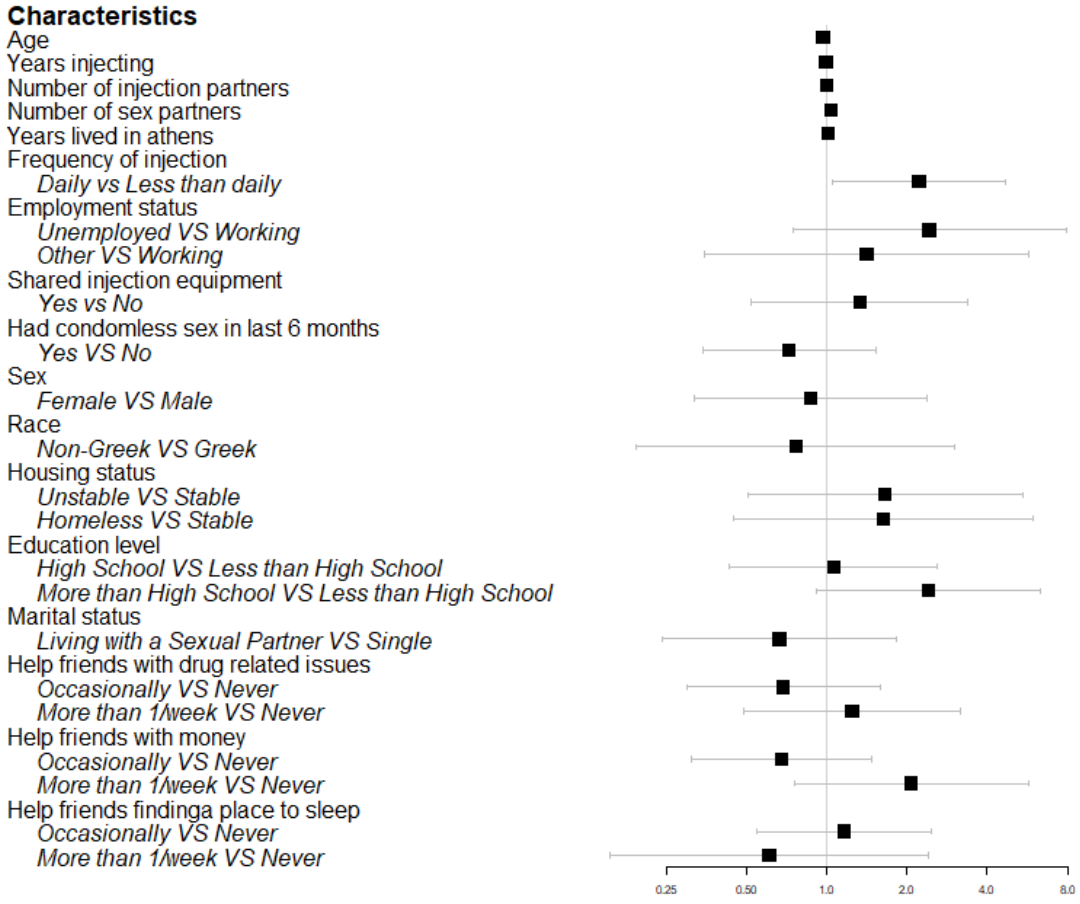
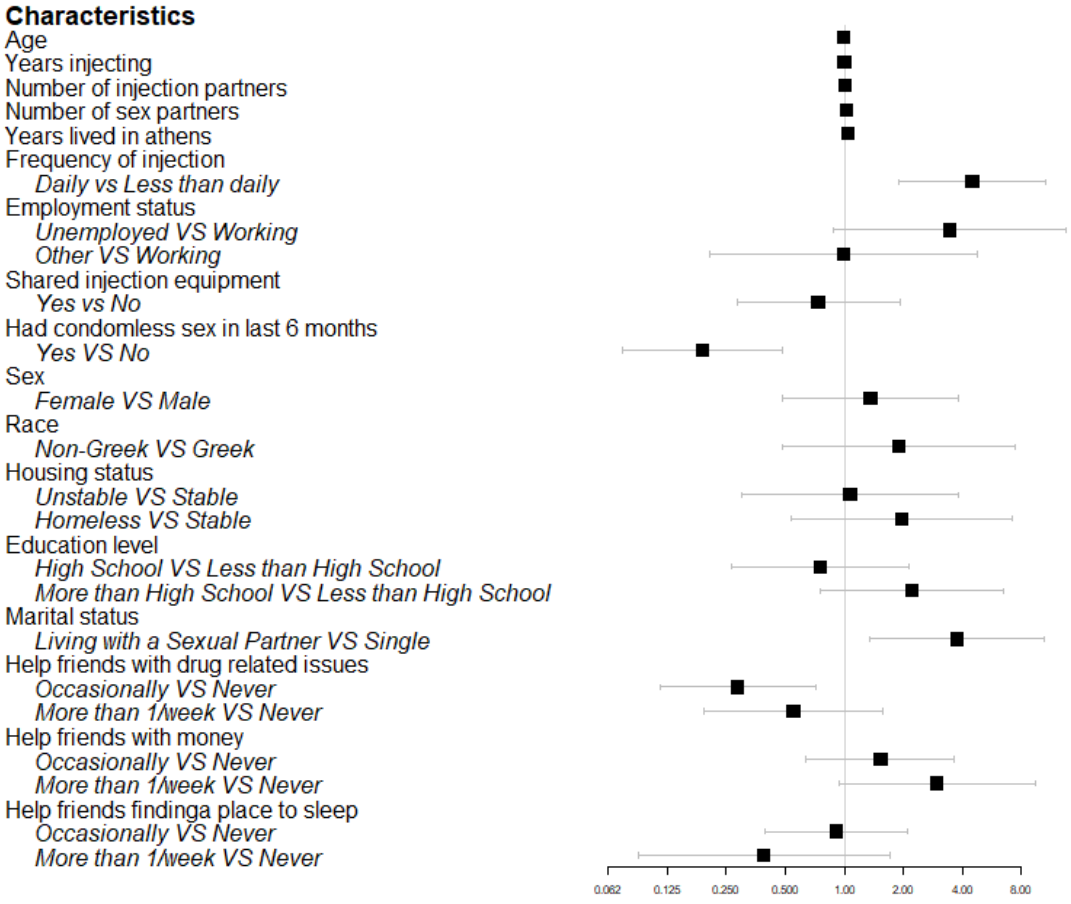


Figure 8. Forrest plot of estimated odds ratios for the association between eigenvector centrality in the upper quartile and individual characteristics among participants Enrolled in the Transmission Reduction Intervention Project, Athens, Greece, 2013-2015 (N = 231)



APPENDICES

Appendix 1 Definitions of centrality measures

Basic network definitions

In order to define the centrality measures there is a necessary level of context needed from basic network theory. A network is a two-part data structure consisting of nodes and edges. Nodes represent points of interest in the network, such as individuals or locations, while edges represent the connections between the nodes, such as friendship or a road between two locations. Two nodes are considered adjacent if they are connected by a single edge. A path is a series of edges and nodes which connect two points on the graph without repeating any nodes. Paths are commonly used to measure distance on a network with the length of a path being equal to the number of edges in the path. By convention the length of the shortest possible path between two nodes, commonly called the geodesic, is the length of the shortest path between those nodes. These shortest paths are often used is network centrality.

Closeness centrality

Closeness centrality is based on the distance between a given node and all other nodes in the network. It is formally defined as the inverse of the sum of the distance between a node and all other nodes in the network and can be calculated using this formula.

$$C_k = \frac{1}{\sum_i^n d(p_i, p_k)}$$

Where $d(p_i, p_k)$ is the length of the shortest path between node i and node k. This measure is partially a function of network size so a rescaling function has been defined to convert it to a size independent measure to allow comparison between networks using the following formula.

$$C_k' = \frac{n-1}{C_k}$$

Betweenness centrality

The betweenness centrality of a node is based on the proportion of shortest paths that it is a part of. First, for each pair of nodes in the network, all of the shortest paths that connect them are identified and the number of shortest paths for that pair are noted. If there is a single shortest path for each pair of nodes then the betweenness centrality of a node is simply the number of those shortest paths that contain that node. However, it is common for pairs of nodes to have more than one shortest path. In this case a nodes betweenness centrality is calculated using the following formula.

$$C_k = \sum_{i}^{n} \sum_{j<i}^{n} \frac{g_{ij}(p_k)}{g_{ij}}$$

Where k is the node of interest, *i* and *j* are other nodes in the network, g_{ij} is the number of shortest paths between *i* and *j*, and $g_{ij}(p_k)$ is the number of paths in g_{ij} that contain node *k*. The resulting score is increased by 1 if the node falls on the only shortest path between nodes *i* and *j* or by the proportion of the shortest paths between *i* and *j* that it falls on if there are multiple shortest paths. The range of C_k is dependent on the size of the network but there is a transformation which scales the range from 0 to 1.

$$C_k' = \frac{2C_k}{n^2 - 3n + 2}$$

This transformation is based on the maximum number of shortest paths in a network as a function of the number of nodes *n*.

Eigenvector centrality

The value of eigenvector centrality is derived from the adjacency matrix of the network. The adjacency matrix is a way of presenting the edges of a network, it is an *n* x *n* matrix *M* where M_{ij} =1 if node *i* has an edge that connects to node *j*. For each node in the network its eigenvector centrality is a corresponding value in the first eigenvector of the adjacency matrix, such that the value for node *i* would be the *i*th value in the eigenvector.

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Appendix 2 Sensitivity Analyses

Appendix 2 Table 1a. Closeness centrality threshold sensitivity analyses

	50%		20%	
Variable	OR	CI	OR	CI
Age (years)	1.035	0.975, 1.097	0.989	0.924, 1.059
Years injecting	0.952	0.907, 0.999	0.980	0.926, 1.037
Self-reported number of injection partners	1.018	0.994, 1.043	1.014	0.994, 1.034
Self-reported number of sex partners	1.008	0.964, 1.054	1.026	0.982, 1.071
Years lived in Athens	1.010	0.975, 1.047	1.005	0.966, 1.046
Frequency of injection over the last 6 months				
Less than daily	Ref		Ref	
At least once per day	4.667	2.286, 9.529	4.831	1.832, 12.744
Employment status				
Working	Ref		Ref	
Unemployed	1.988	0.734, 5.380	3.038	0.690, 13.370
Other (student, homemaker, etc.)	0.452	0.128, 1.593	1.691	0.319, 8.966
Shared injection equipment in the last six months	1.333	0.571, 3.107	0.470	0.168, 1.314
Condomless sex in the last six months	0.349	0.171, 0.713	0.215	0.079, 0.581
Gender				
Male	Ref		Ref	
Female	2.159	0.825, 5.651	1.303	0.412, 4.128
Ethnicity				
Greek	Ref		Ref	
Non-Greek	1.549	0.428, 5.603	1.159	0.282, 4.766
Housing status				
Stable	Ref		Ref	
Unstable	1.238	0.436, 3.513	0.823	0.209, 3.249
Homeless	2.617	0.833, 8.220	1.198	0.296, 4.850

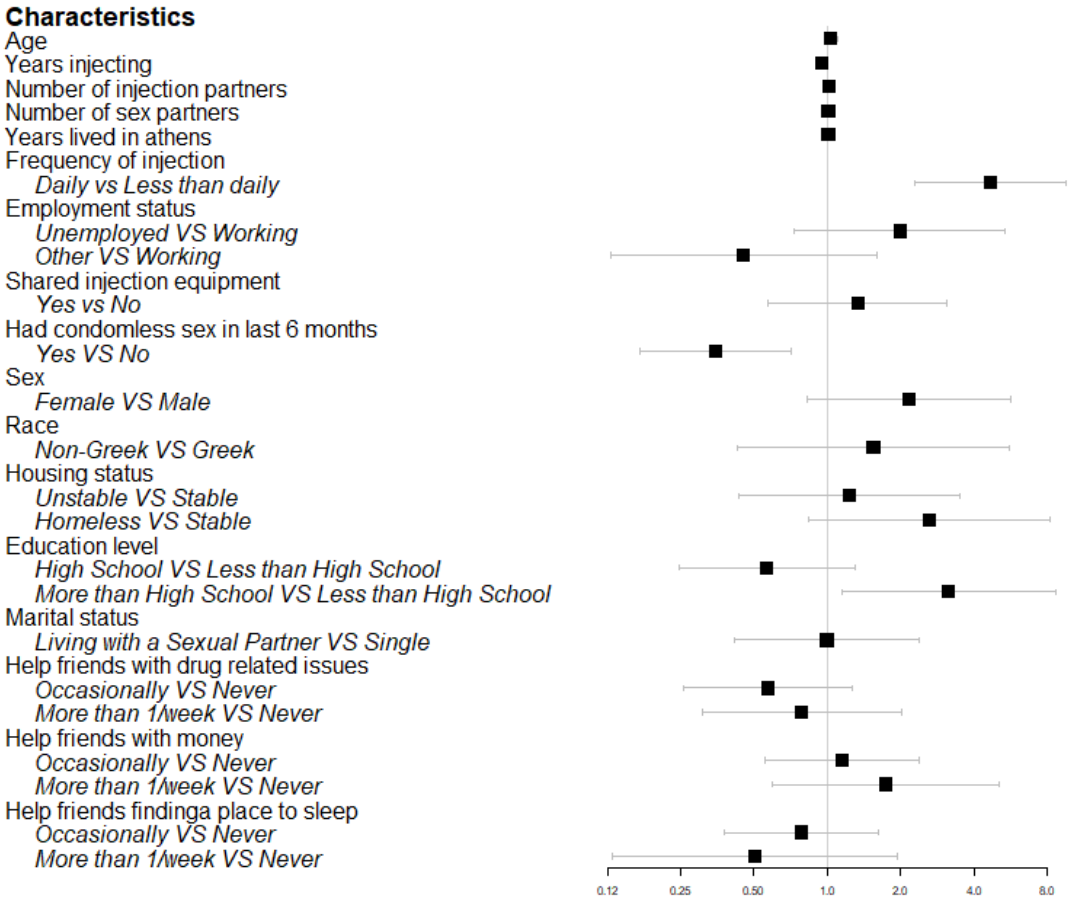
Education				
Less than high school diploma	Ref		Ref	
High school diploma	0.565	0.246, 1.297	4.073	1.392, 11.915
College or other advanced education	3.155	1.145, 8.690	0.697	0.212, 2.296
Relationship status				
Single	Ref		Ref	
Living with partner	0.997	0.414, 2.398	1.868	0.611, 5.711
Helped contacts with finding treatment for substance use issues				
Never	Ref		Ref	
Occasionally	0.570	0.256, 1.271	0.538	0.205, 1.412
At least once per week	0.785	0.306, 2.012	0.819	0.268, 2.502
Helped contacts with financial support				
Never	Ref		Ref	
Occasionally	1.151	0.554, 2.389	0.966	0.386, 2.416
At least once per week	1.747	0.597, 5.110	2.331	0.731, 7.435
Helped contacts with finding a place to sleep				
Never	Ref		Ref	
Occasionally	0.780	0.377, 1.613	1.257	0.510, 3.097
At least once per week	0.505	0.131, 1.941	0.622	0.133, 2.915

Appendix 2 Table 1b. Closeness centrality threshold sensitivity analyses

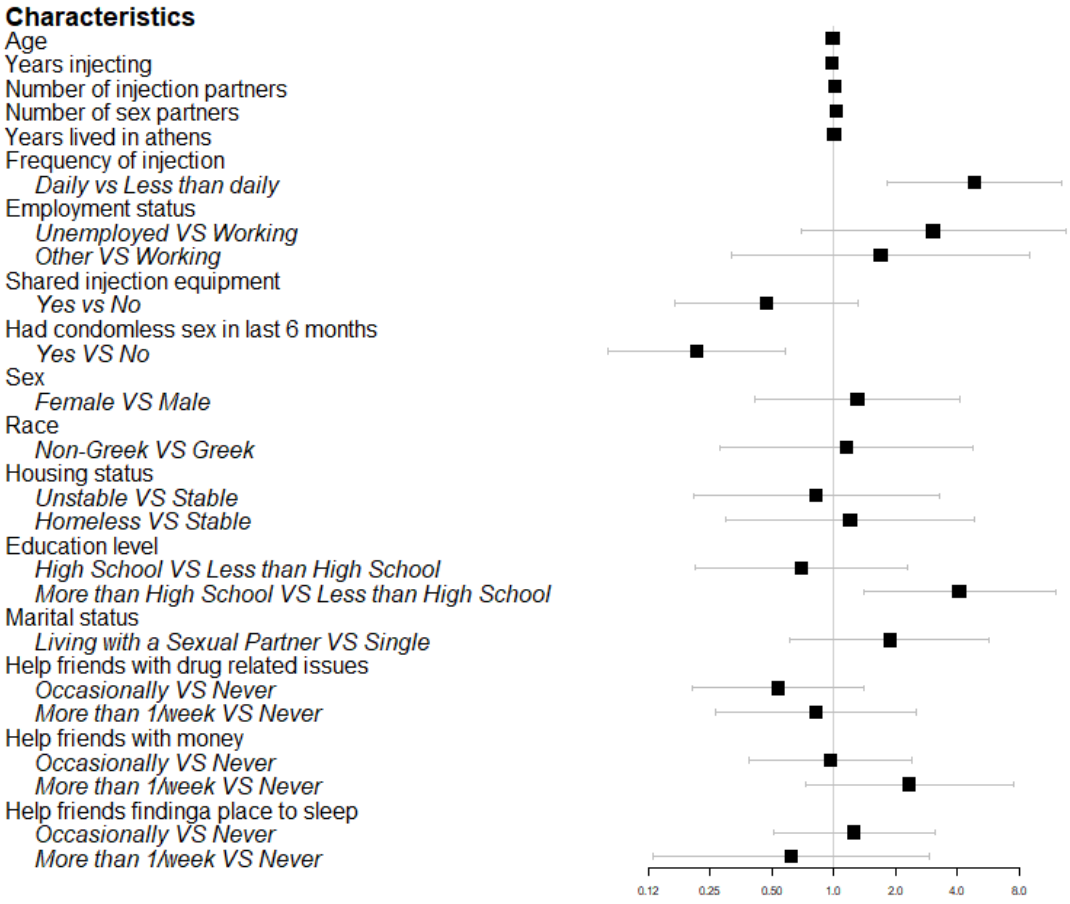
	10%	
Variable	OR	CI
Age (years)	0.931	0.924, 1.059
Years injecting	0.997	0.926, 1.037
Self-reported number of injection partners	0.990	0.994, 1.034
Self-reported number of sex partners	1.017	0.982, 1.071
Years lived in Athens	1.016	0.966, 1.046
Frequency of injection over the last 6 months		
Less than daily	Ref	
At least once per day	1.201	1.832, 12.744
Employment status		
Working	Ref	
Unemployed	1.033	0.690, 13.370
Other (student, homemaker, etc.)	1.098	0.319, 8.966
Shared injection equipment in the last six months	0.509	0.168, 1.314
Condomless sex in the last six months	0.297	0.079, 0.581
Gender		
Male	Ref	
Female	1.286	0.412, 4.128
Ethnicity		
Greek	Ref	
Non-Greek	1.233	0.282, 4.766
Housing status		
Stable	Ref	
Unstable	1.099	0.209, 3.249
Homeless	9.044	0.296, 4.850
Education		
Less than high school diploma	Ref	
High school diploma	4.738	1.392, 11.915
College or other advanced education	0.736	0.212, 2.296

Relationship status		
Single	Ref	
Living with partner	0.739	0.611, 5.711
Helped contacts with finding treatment for substance use issues		
Never	Ref	
Occasionally	0.657	0.205, 1.412
At least once per week	0.523	0.268, 2.502
Helped contacts with financial support		
Never	Ref	
Occasionally	1.244	0.386, 2.416
At least once per week	3.565	0.731, 7.435
Helped contacts with finding a place to sleep		
Never	Ref	
Occasionally	0.938	0.510, 3.097
At least once per week	0.396	0.133, 2.915

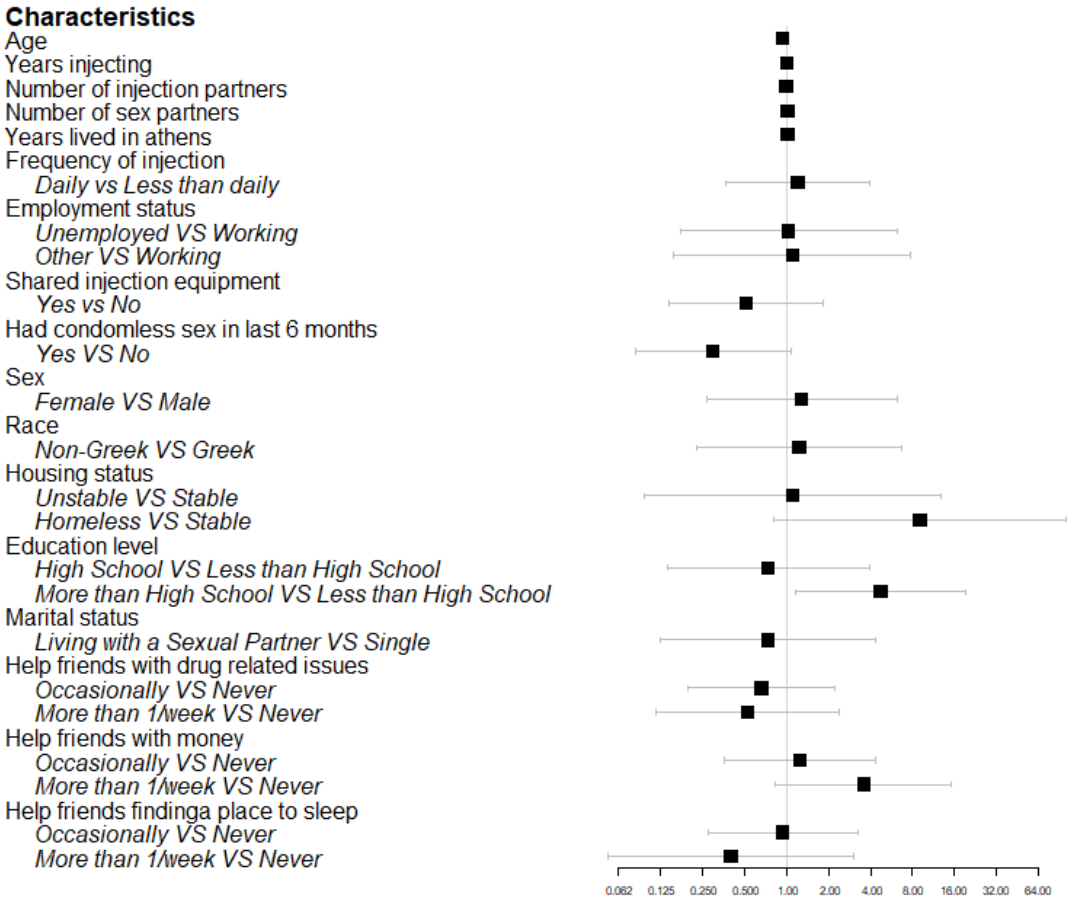
Appendix 2 Figure 1 Forrest plot of 50% threshold high closeness centrality



Appendix 2 Figure 2 Forrest plot of 20% threshold high closeness centrality



Appendix 2 Figure 3 Forrest plot of 10% threshold high closeness centrality



Appendix 2 table 2a Betweenness centrality threshold sensitivity analyses

	50%		20%	
Variable	OR	CI	OR	CI
Age (years)	0.970	0.920, 1.023	0.955	0.895, 1.019
Years injecting	0.989	0.948, 1.031	0.992	0.941, 1.046
Self-reported number of injection partners	1.004	0.986, 1.022	0.996	0.975, 1.018
Self-reported number of sex partners	1.001	0.961, 1.043	1.005	0.965, 1.046
Years lived in Athens	1.011	0.980, 1.044	1.019	0.980, 1.060
Frequency of injection over the last 6 months				
Less than daily	Ref		Ref	
At least once per day	1.841	0.975, 3.475	1.942	0.833, 4.274
Employment status				
Working	Ref		Ref	
Unemployed	1.659	0.677, 4.066	1.707	0.517, 5.636
Other (student, homemaker, etc.)	0.901	0.290, 2.801	1.316	0.319, 5.428
Shared injection equipment in the last six months	1.403	0.646, 3.047	1.056	0.407, 2.743
Condomless sex in the last six months	0.520	0.272, 0.994	0.671	0.304, 1.482
Gender				
Male	Ref		Ref	
Female	2.960	1.217, 7.199	1.134	0.402, 3.197
Ethnicity				
Greek	Ref		Ref	
Non-Greek	0.392	0.122, 1.262	0.558	0.123, 2.524
Housing status				
Stable	Ref		Ref	
Unstable	0.889	0.346, 2.286	1.072	0.318, 3.612
Homeless	1.231	0.425, 3.566	1.483	0.399, 5.506
Education				
Less than high school diploma	Ref		Ref	
High school diploma	1.309	0.537, 3.192	2.354	0.845, 6.557
College or other advanced education	0.567	0.269, 1.199	0.989	0.374, 2.619
Relationship status				
Single	Ref		Ref	
Living with partner	0.857	0.386, 1.903	0.568	0.186, 1.733
Helped contacts with				

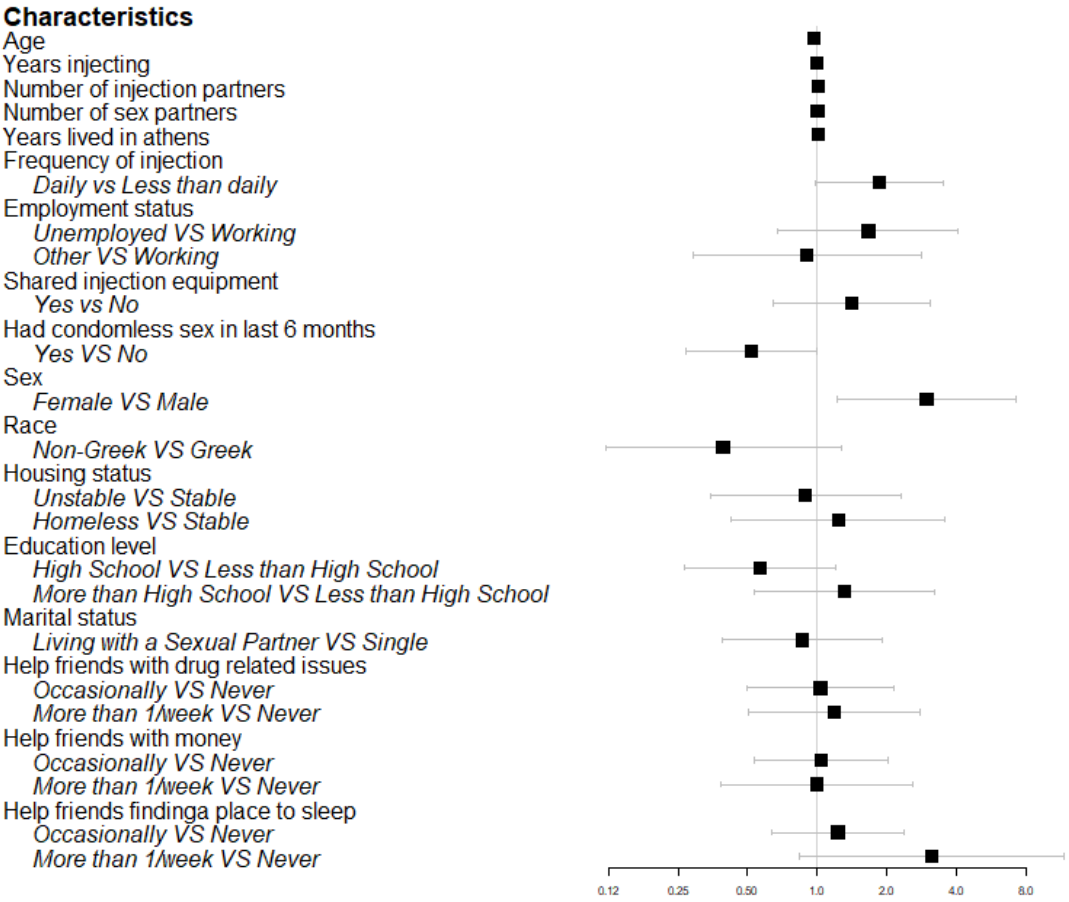
finding treatment for substance use issues				
Never	Ref		Ref	
Occasionally	1.030	0.499, 2.127	0.686	0.284, 1.657
At least once per week	1.182	0.502, 2.784	0.935	0.351, 2.488
Helped contacts with financial support				
Never	Ref		Ref	
Occasionally	1.037	0.532, 2.023	0.752	0.327, 1.731
At least once per week	0.992	0.381, 2.583	2.427	0.865, 6.806
Helped contacts with finding a place to sleep				
Never	Ref		Ref	
Occasionally	1.225	0.639, 2.350	1.399	0.626, 3.127
At least once per week	3.099	0.833, 11.527	0.733	0.177, 3.036

Appendix 2 table 2b Betweenness centrality threshold sensitivity analyses

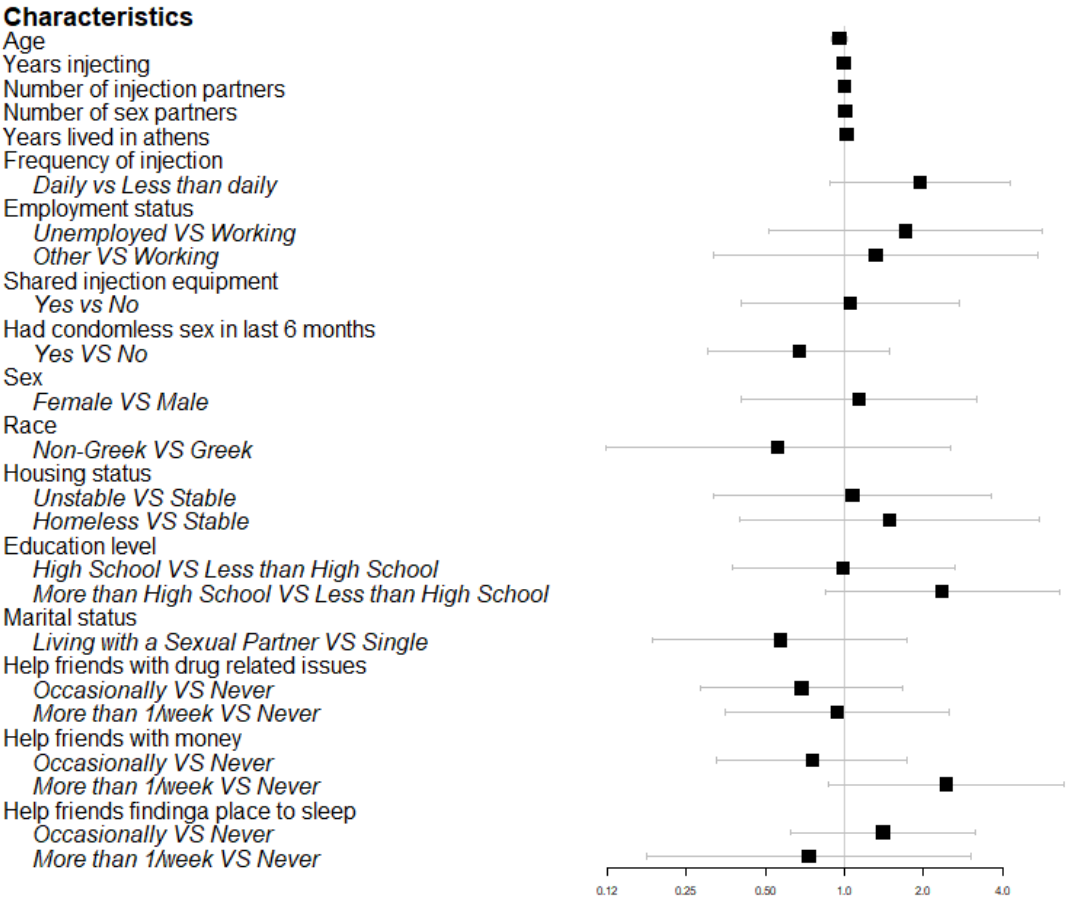
	10%	
Variable	OR	CI
Age (years)	0.948	0.863, 1.040
Years injecting	1.014	0.935, 1.100
Self-reported number of injection partners	1.007	0.980, 1.035
Self-reported number of sex partners	1.063	1.000, 1.131
Years lived in Athens	0.996	0.945, 1.050
Frequency of injection over the last 6 months		
Less than daily	Ref	
At least once per day	1.698	0.546, 5.280
Employment status		
Working	Ref	
Unemployed	1.616	0.312, 8.366
Other (student, homemaker, etc.)	1.890	0.267, 13.392
Shared injection equipment in the last six months	1.217	0.281, 5.276
Condomless sex in the last six months	0.344	0.105, 1.127
Gender		
Male	Ref	
Female	0.148	0.016, 1.369
Ethnicity		
Greek	Ref	
Non-Greek	0.207	0.023, 1.891
Housing status		
Stable	Ref	
Unstable	0.259	0.044, 1.518
Homeless	0.329	0.050, 2.174
Education		
Less than high school diploma	Ref	
High school diploma	6.151	1.541, 24.562
College or other advanced education	0.923	0.209, 4.085
Relationship status		
Single	Ref	
Living with partner	0.205	0.022, 1.930

Helped contacts with finding treatment for substance use issues		
Never	Ref	
Occasionally	0.947	0.267, 3.362
At least once per week	0.988	0.238, 4.095
Helped contacts with financial support		
Never	Ref	
Occasionally	0.569	0.171, 1.900
At least once per week	2.146	0.557, 8.265
Helped contacts with finding a place to sleep		
Never	Ref	
Occasionally	1.569	0.500, 4.927
At least once per week	0.548	0.070, 4.316

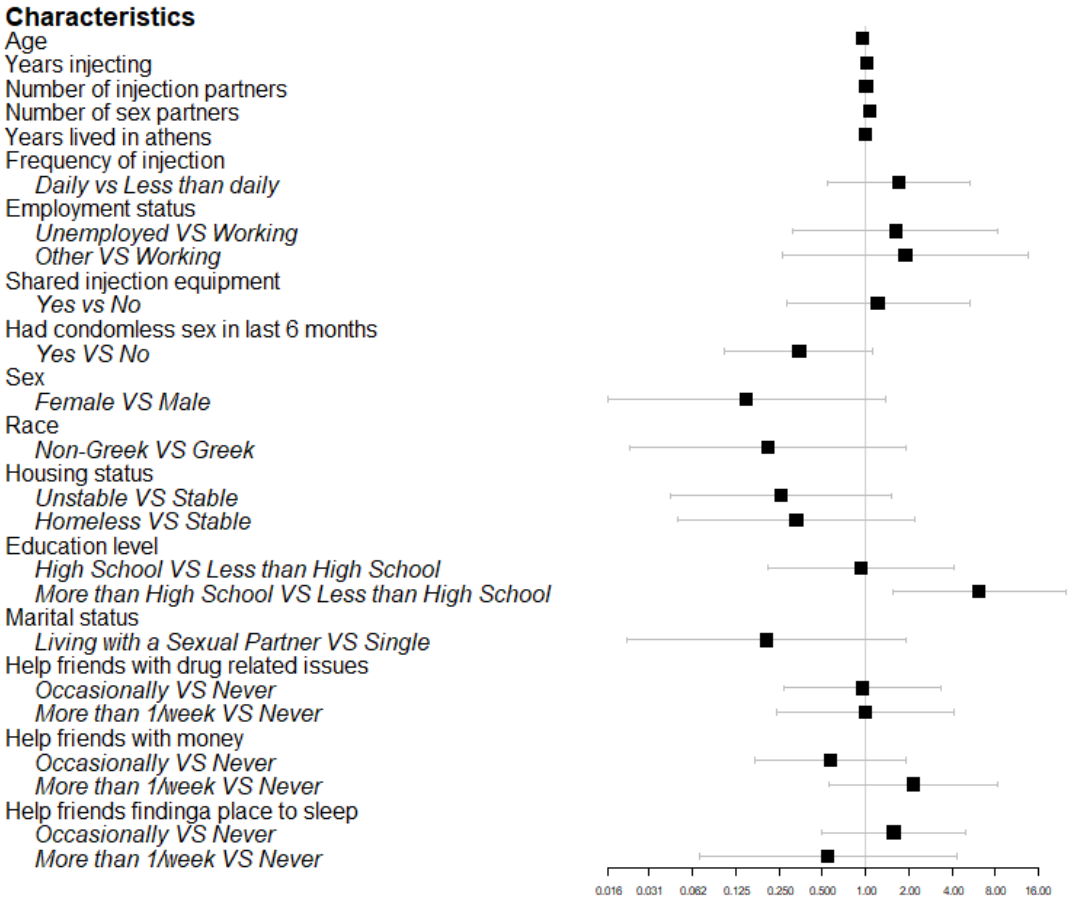
Appendix 2 Figure 4 Forrest plot of 50% threshold high betweenness centrality



Appendix 2 Figure 5 Forrest plot of 20% threshold high betweenness centrality



Appendix 2 Figure 6 Forrest plot of 10% threshold high betweenness centrality



Appendix 2 table 3a Eigenvector centrality threshold sensitivity analyses

	50%		20%	
Variable	OR	CI	OR	CI
Age (years)	1.033	0.973, 1.096	0.971	0.904, 1.044
Years injecting	0.963	0.917, 1.012	0.999	0.945, 1.056
Self-reported number of injection partners	1.016	0.992, 1.041	0.994	0.971, 1.017
Self-reported number of sex partners	1.021	0.976, 1.069	1.023	0.979, 1.070
Years lived in Athens	1.009	0.974, 1.046	1.062	1.012, 1.115
Frequency of injection over the last 6 months				
Less than daily	Ref		Ref	
At least once per day	5.806	2.774, 12.155	5.385	2.048, 14.158
Employment status				
Working	Ref		Ref	
Unemployed	2.139	0.753, 6.076	1.755	0.433, 7.110
Other (student, homemaker, etc.)	0.463	0.127, 1.692	0.722	0.140, 3.726
Shared injection equipment in the last six months	1.188	0.501, 2.816	0.548	0.198, 1.518
Condomless sex in the last six months	0.189	0.088, 0.408	0.227	0.083, 0.617
Gender				
Male	Ref		Ref	
Female	2.380	0.891, 6.354	1.605	0.508, 5.077
Ethnicity				
Greek	Ref		Ref	
Non-Greek	1.747	0.483, 6.320	3.207	0.712, 14.454
Housing status				
Stable	Ref		Ref	
Unstable	1.420	0.489, 4.121	1.300	0.310, 5.452
Homeless	2.233	0.697, 7.153	3.158	0.729, 13.685
Education				
Less than high school diploma	Ref		Ref	
High school diploma	1.979	0.733, 5.341	1.381	0.422, 4.519
College or other advanced education	0.901	0.387, 2.098	0.631	0.195, 2.042
Relationship status				

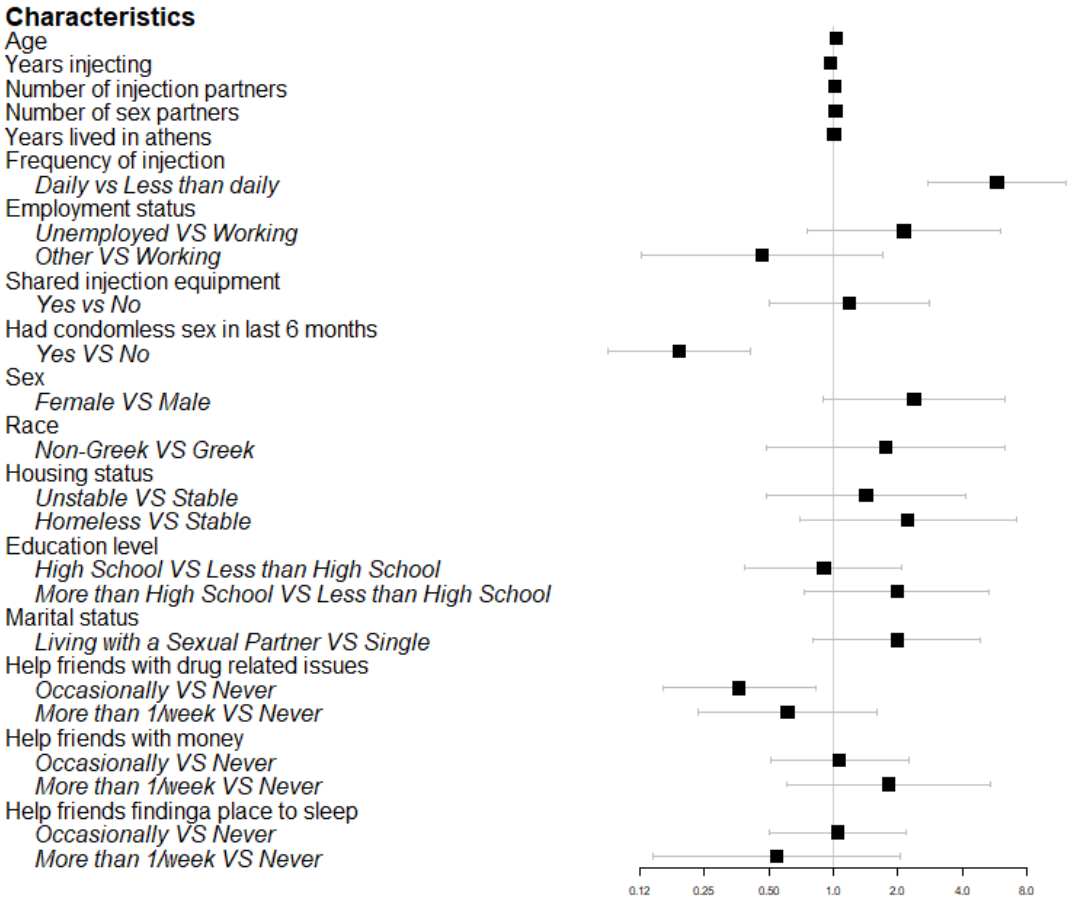
Single	Ref		Ref	
Living with partner	1.982	0.804, 4.889	4.086	1.337, 12.486
Helped contacts with finding treatment for substance use issues				
Never	Ref		Ref	
Occasionally	0.362	0.159, 0.825	0.487	0.189, 1.257
At least once per week	0.611	0.233, 1.604	0.593	0.189, 1.862
Helped contacts with financial support				
Never	Ref		Ref	
Occasionally	1.070	0.509, 2.248	0.814	0.318, 2.083
At least once per week	1.820	0.610, 5.436	1.965	0.583, 6.621
Helped contacts with finding a place to sleep				
Never	Ref		Ref	
Occasionally	1.047	0.499, 2.197	1.092	0.443, 2.689
At least once per week	0.545	0.144, 2.056	0.206	0.036, 1.171

Appendix 2 table 3b Eigenvector centrality threshold sensitivity analyses

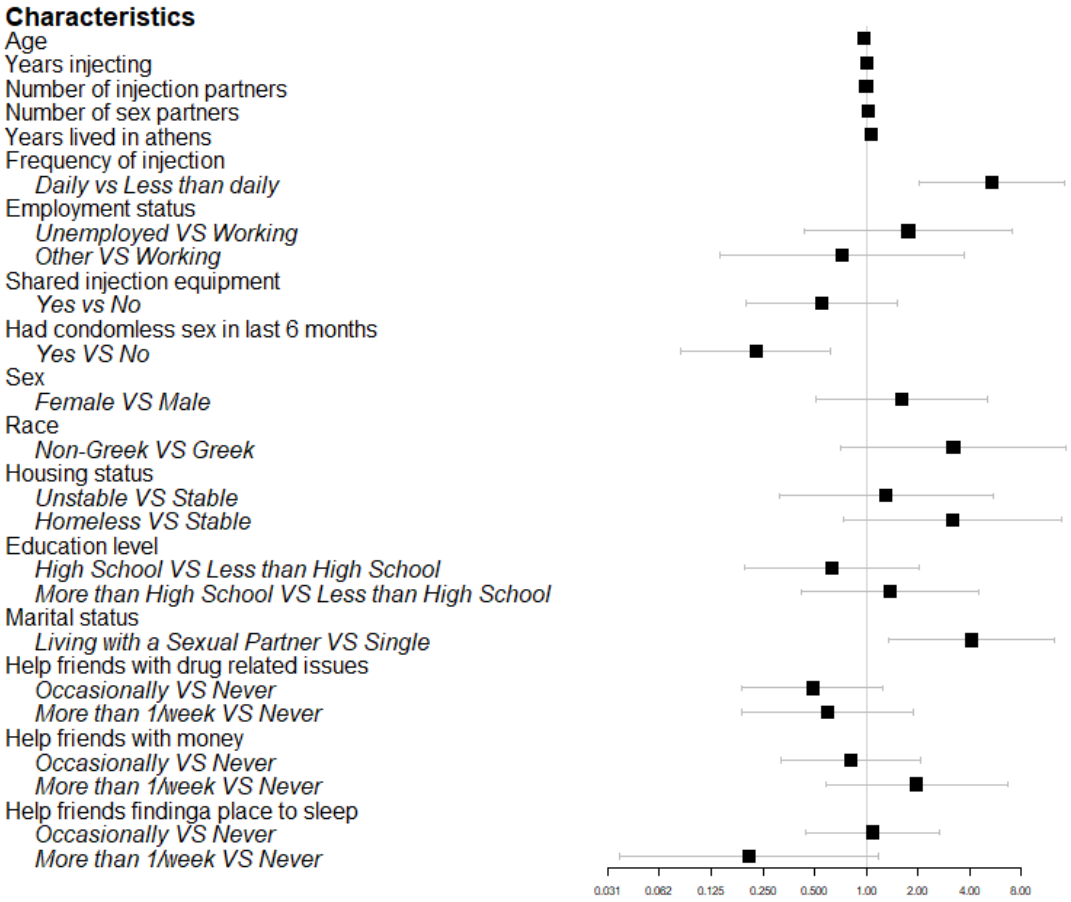
	10%	
Variable	OR	CI
Age (years)	0.976	0.868, 1.097
Years injecting	1.012	0.938, 1.091
Self-reported number of injection partners	1.000	0.968, 1.033
Self-reported number of sex partners	1.013	0.950, 1.079
Years lived in Athens	1.106	1.019, 1.201
Frequency of injection over the last 6 months		
Less than daily	Ref	
At least once per day	9.505	2.048
Employment status		
Working	Ref	
Unemployed	3.037	0.387, 23.860
Other (student, homemaker, etc.)	0.735	0.075, 7.217
Shared injection equipment in the last six months	0.180	0.044, 0.733
Condomless sex in the last six months	0.164	0.035, 0.779
Gender		
Male	Ref	
Female	2.961	0.578, 15.158
Ethnicity		
Greek	Ref	
Non-Greek	4.454	0.502, 39.504
Housing status		
Stable	Ref	
Unstable	0.128	0.017, 0.986
Homeless	0.669	0.100, 4.467
Education		
Less than high school diploma	Ref	
High school diploma	3.190	0.662, 15.372
College or other advanced education	0.627	0.093, 4.208

Relationship status		
Single	Ref	
Living with partner	1.087	0.200, 5.894
Helped contacts with finding treatment for substance use issues		
Never	Ref	
Occasionally	1.843	0.386, 8.797
At least once per week	0.893	0.140, 5.721
Helped contacts with financial support		
Never	Ref	
Occasionally	1.283	0.291, 5.654
At least once per week	5.219	0.868, 31.396
Helped contacts with finding a place to sleep		
Never	Ref	
Occasionally	0.915	0.237, 3.522
At least once per week	0.168	0.015, 1.890

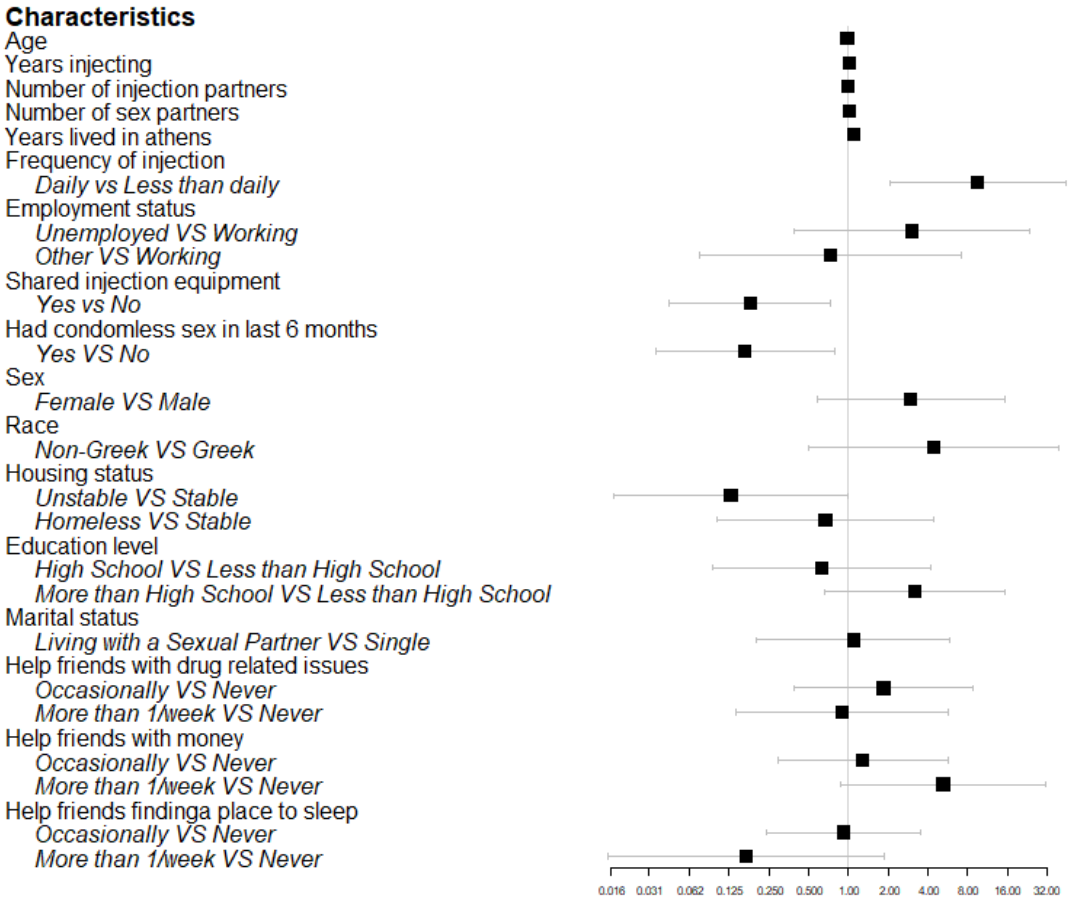
Appendix 2 Figure 7 Forrest plot of 50% threshold high eigenvector centrality



Appendix 2 Figure 8 Forrest plot of 20% threshold high eigenvector centrality

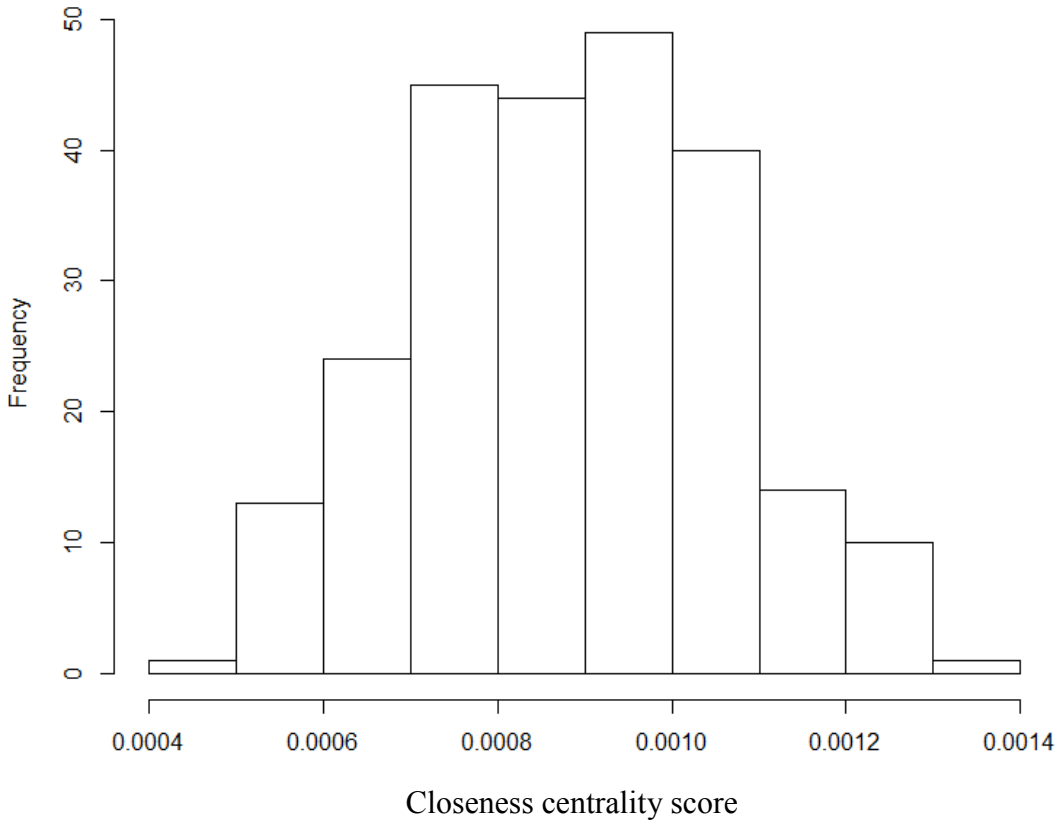


Appendix 2 Figure 9 Forrest plot of 10% threshold high eigenvector centrality

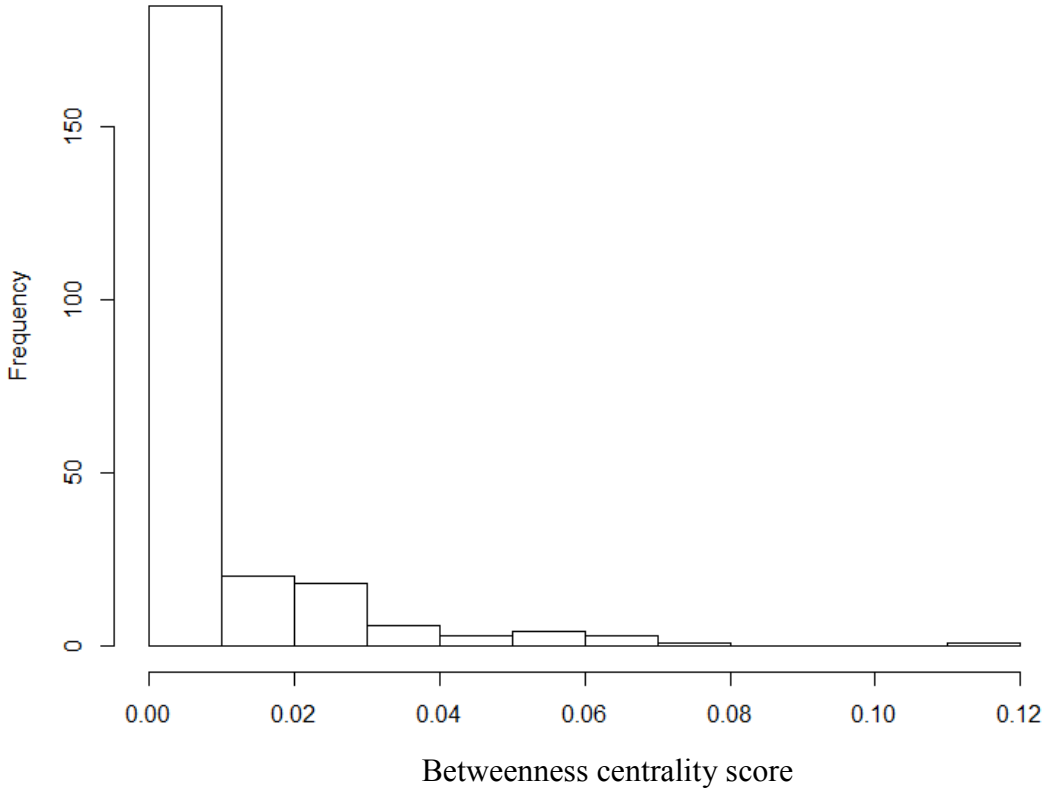


Appendix 3. Centrality Distributions

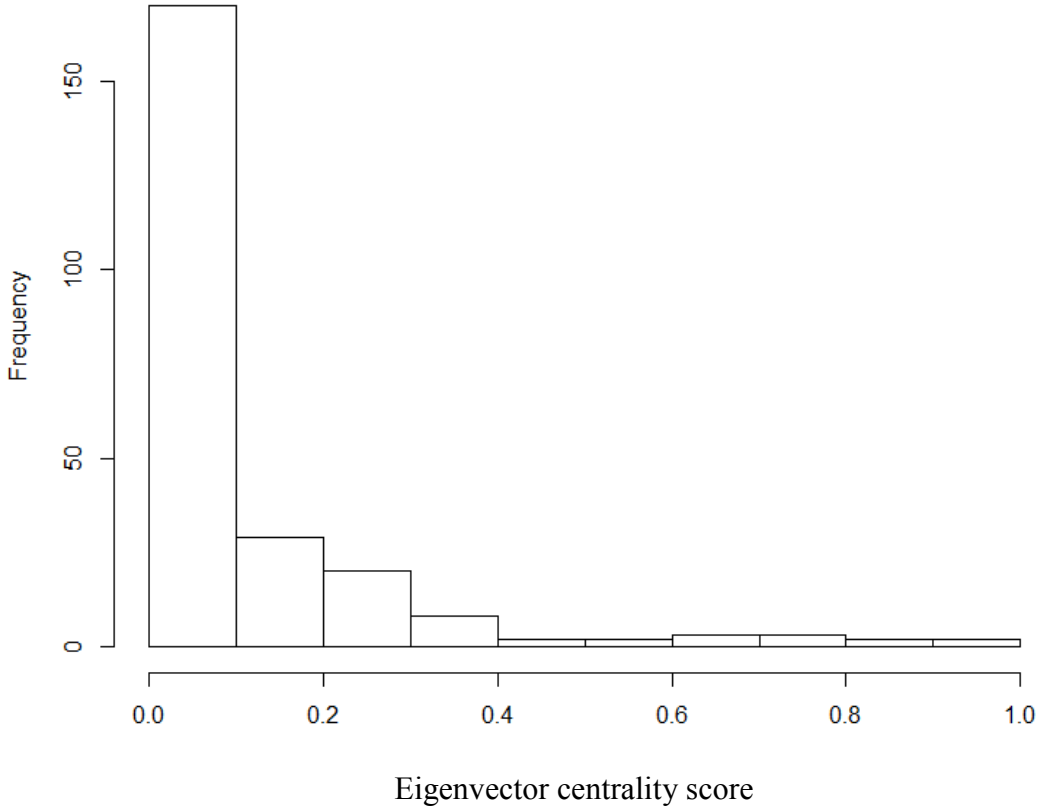
Appendix 3 Figure 1. Histogram of closeness centrality of the giant component of TRIP



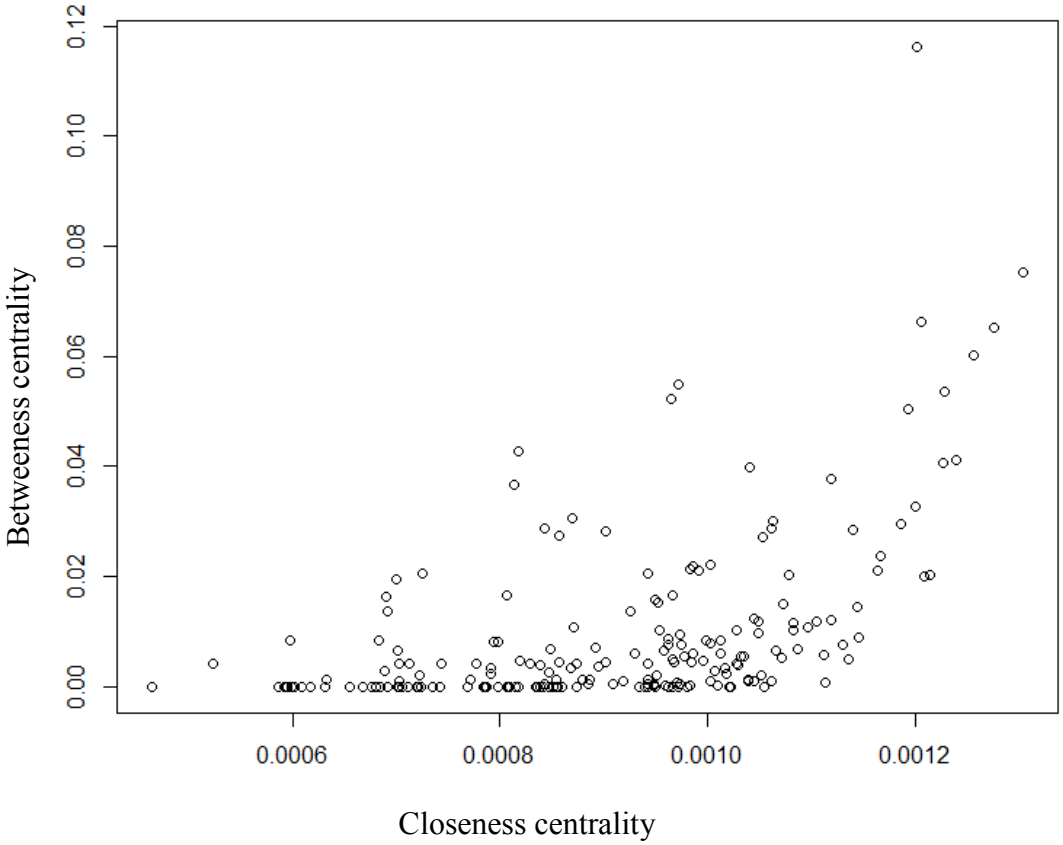
Appendix 3 Figure 2. Histogram of Betweenness centrality of the giant component of TRIP



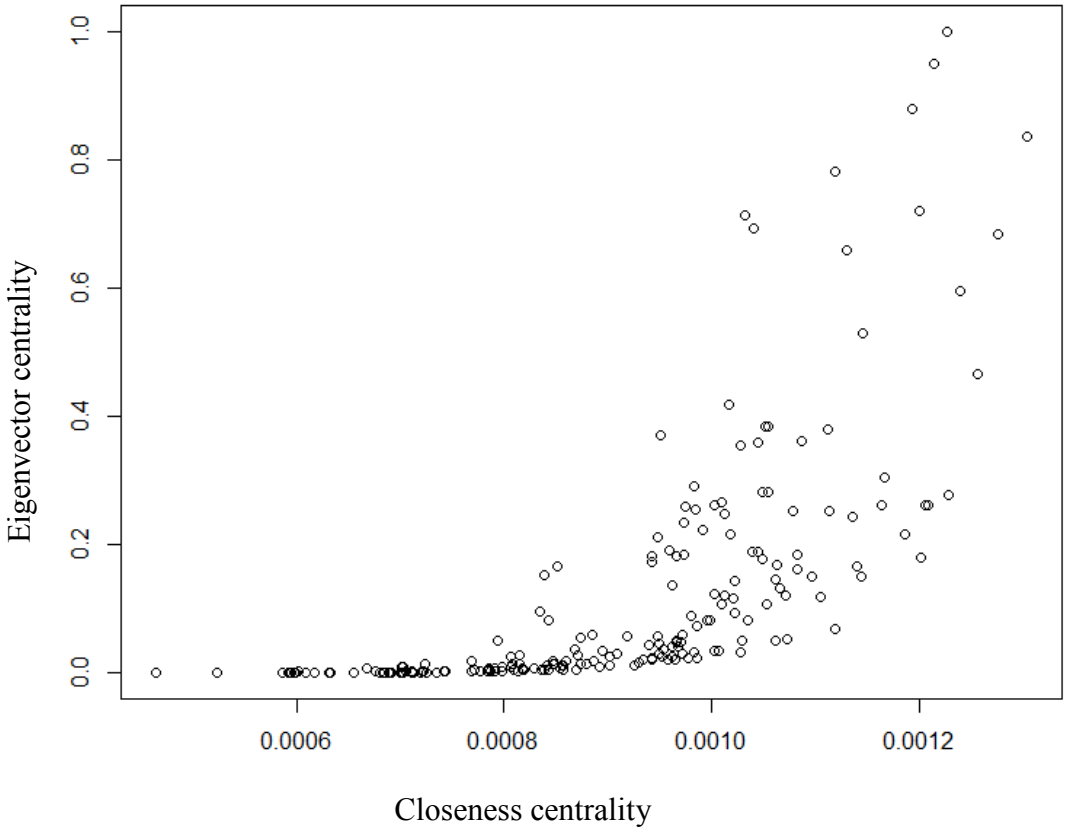
Appendix 3 Figure 3. Histogram of eigenvector centrality of the giant component of TRIP



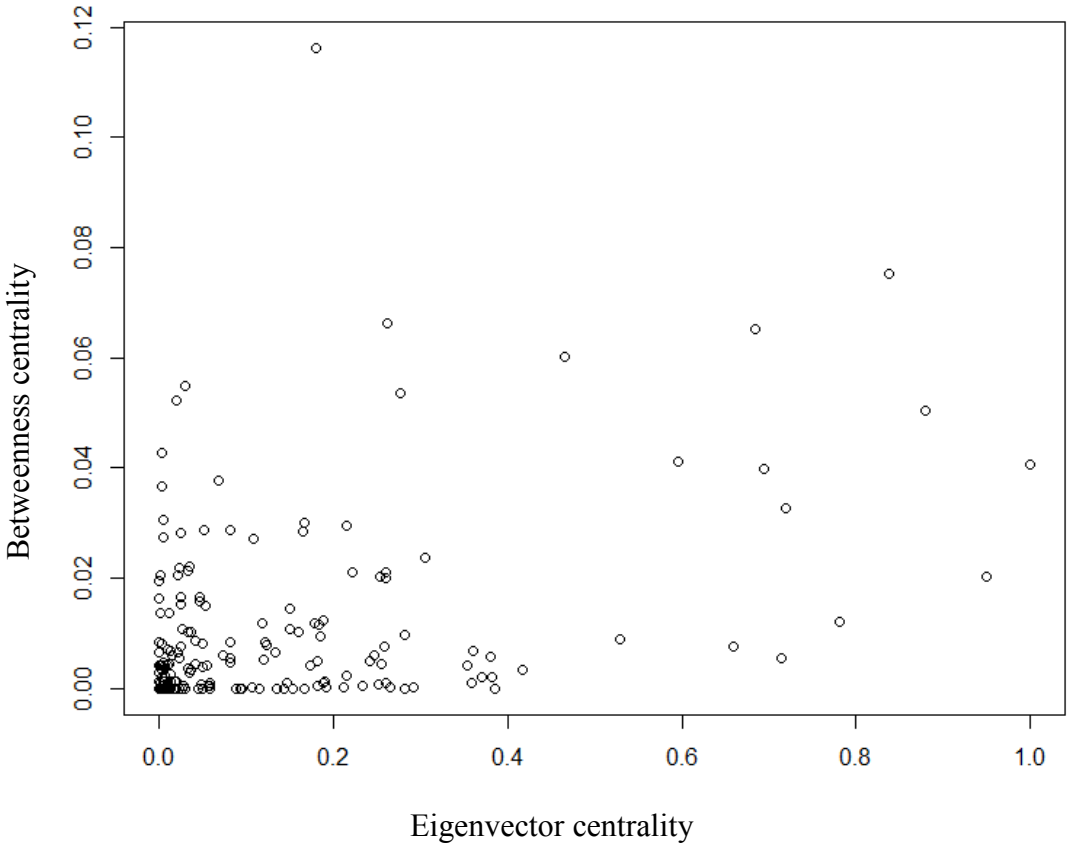
Appendix 3 Figure 4. Scatterplot of closeness and betweenness centrality in the ginat component of TRIP



Appendix 3 Figure 4. Scatterplot of closeness and betweenness centrality in the giant component of TRIP



Appendix 3 Figure 5. Scatterplot of eigenvector and betweenness centrality in the giant component of TRIP



Appendix 3 Table 1. Correlation matrix of Network centrality measures in the study sample

	Closeness	Betweenness	Eigenvector
Closeness	1.00	0.52	0.68
Betweenness	0.52	1.00	0.43
Eigenvector	0.68	0.43	1.00

Appendix 3 Table 2. Cross tabulation of closeness and betweenness centrality quartiles

	Betweenness 0-25%	Betweenness 26-50%	Betweenness 51-75%	Betweenness 76-100%
Closeness 0-25%	45	2	8	4
Closeness 26-50%	32	2	17	7
Closeness 51-75%	9	14	20	15
Closeness 76-100%	4	6	13	33

Appendix 3 Table 3. Cross tabulation of closeness and eigenvector centrality quartiles

	Eigenvector 0-25%	Eigenvector 26-50%	Eigenvector 51-75%	Eigenvector 76-100%
Closeness 0-25%	45	14	0	0
Closeness 26-50%	13	34	9	2
Closeness 51-75%	0	10	35	13
Closeness 76-100%	0	0	14	42

Appendix 3 Table 3. Cross tabulation of betweenness and eigenvector centrality quartiles

	Eigenvector 0-25%	Eigenvector 26-50%	Eigenvector 51-75%	Eigenvector 76-100%
Betweenness 0-25%	42	35	11	2
Betweenness 26-50%	2	2	8	12
Betweenness 51-75%	9	17	18	14
Betweenness 76-100%	5	4	21	29

Appendix 4 Supplementary Information on the Study Sample

Appendix 4. Table 1. Substance use reported at Baseline Visit by Participants Enrolled in the Transmission Reduction Intervention Project, Athens, Greece, 2013-2015 (N = 231)

	Reported use in the last 6 months	Reported daily use in the last 6 months	Reported injection use in the last 6 months	Reported daily injection use in the last 6 months
Any other substances (specify)	222 (96%)	160(69%)	147(64%)	82(35%)
Cocaine	186(81%)	49(21%)	168(73%)	45(19%)
Cannabis	171(74%)	48(21%)	0(0%)	0(0%)
Heroin	165(71%)	89(39%)	119(52%)	50(22%)
Speedball	148(64%)	54(23%)	130(56%)	53(23%)
Alcohol	138(60%)	14(6%)	0(0%)	0(0%)
Street Buprenorphine or Methadone	104(45%)	6(3%)	7(3%)	0(0%)
Prescription Pain Killers including narcotics or Morphine	60(26%)	4(2%)	0(0%)	0(0%)
Methampheta mine	50(22%)	5(2%)	9(4%)	2(1%)
Crack	31(13%)	3(1%)	2(1%)	1(1%)

Ecstasy	16(7%)	0(0%)	0(0%)	0(0%)
Psychedelics	14(6%)	0(0%)	0(0%)	0(0%)
Amphetamines	12(5%)	1(1%)	4(2%)	1(1%)
Opium	3(1%)	0(0%)	1(1%)	0(0%)
Poppers	3(1%)	0(0%)	0(0%)	0(0%)
Viagra, Levitra, Cialis or similar drugs	3(1%)	0(0%)	0(0%)	0(0%)
Desomorphine	1(1%)	1(1%)	0(0%)	0(0%)
Cathinone	0(0%)	0(0%)	0(0%)	0(0%)
Steroids	0(0%)	0(0%)	0(0%)	0(0%)
Cough Syrup with codeine and promethazine	0(0%)	0(0%)	0(0%)	0(0%)